

Modified Release Formulations of at Least One Form of Tramadol

RELATED APPLICATIONS

This application claims priority to U.S. Provisional No. 60/357,851, filed on  
5 February 21, 2002 which is incorporated by reference herein.

FIELD OF INVENTION

The present invention relates to modified release formulations for oral  
administration, to processes for their preparation and to their medical use. In  
10 particular, the present invention relates to modified release formulations of at  
least one form of tramadol, selected from the group consisting of tramadol,  
racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts  
thereof and combinations thereof.

BACKGROUND OF THE INVENTION

15 Tramadol, which was first described in United States Patent No. 3,652,589,  
is a class of analgesic cycloalkanol-substituted phenol esters having a basic amine  
group in the cycloalkyl ring and having the chemical name *trans*-( $\pm$ )-2-  
[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol. Tramadol is  
believed to produce an analgesic effect through a mechanism that is neither fully  
20 opioid-like nor non-opioid-like because clinical data suggests that tramadol lacks  
many of the typical side effects of opioid antagonists such as respiratory  
depression, constipation, tolerance and abuse liability but can produce hot  
flashes and sweating. Due to the combination of non-opioid and opioid activity,  
tramadol is a very unique analgesic and many attempts have been made to  
25 prepare oral formulations of the drug.

Conventional or immediate release preparations in the form of tablets,  
capsules, drops and suppositories containing tramadol, or more particularly its  
hydrochloride salt, have been commercially available for many years for use in  
the treatment of moderate to severe pain. The clinical efficacy of immediate  
30 release tramadol preparations has been well established in numerous single dose  
and multiple dose studies, with 70% to 90% of patients obtaining satisfactory

pain relief depending on the etiology of the pain. Immediate release tramadol preparations have demonstrated efficacy in obstetrical, gynecologic, orthopedic, abdominal and oral surgery. Immediate release tramadol preparations have also been studied in long-term clinical trials in patients with chronic pain of varying  
5 etiology, including low-back pain, osteoarthritis, cancer pain, neuropathic pain and orthopedic pain.

Immediate release tramadol preparations, however, do not provide a controlled release of the tramadol. For example, an immediate release oral formulation of tramadol is commercially available in the United States, from  
10 McNeil Pharmaceuticals under the tradename ULTRAM® as tramadol hydrochloride tablets. The 53<sup>rd</sup> Edition of the Physician's Desk Reference, copyright 1999, p. 2255, states that peak plasma levels of tramadol for the ULTRAM® product occur at about 1.6 hours after a single oral dose (100 mg) and at about 2.3 hours after multiple oral dosing (100 mg q.i.d). The short elimination  
15 half-life of tramadol necessitates dosing of patients with immediate release tramadol preparations every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain.

To overcome the difficulties associated with the required dosing frequency of immediate release tramadol preparations, various attempts have  
20 been made to formulate tramadol into modified release formulations. For example, see United States Patent Nos. 5,395,626, 5,474,786, 5,645,858, 5,478,577, 5,591,452, 6,254,887, 5,601,842, 5,580,578, 5,639,476, 5,811,126, 5,849,240, 5,891,471, 5,965,163, 5,958,452, 5,965,161, 5,478,577, 5,580,578, 5,648,096, 5,672,360, 5,811,126, 5,879,705, 5,968,551, 5,980,941, 6,068,858, 6,077,532, 6,077,533 and 6,254,887. Such  
25 modified release tramadol preparations purport to control the rate of release of tramadol within the gastrointestinal tract, with the purported result that tramadol is delivered at a specific, predetermined rate.

#### SUMMARY OF THE INVENTION

It is an object of the present invention to prepare a modified release  
30 pharmaceutical composition comprising at least one form of tramadol.

It is a further object of the present invention to prepare a modified release pharmaceutical composition comprising at least one form of tramadol wherein the composition is suitable for oral administration to patients which provides effective relief from pain.

5 Further and other objects of the present invention will be realized by those skilled in the art from the following summary of the invention and detailed description of embodiments thereof.

In accordance with one aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for  
10 once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in combination with at least one pharmaceutically acceptable excipient, wherein the pharmaceutical composition when orally administered to a patient, induces a  
15 statistically significant lower mean fluctuation index in the plasma than an immediate release composition of the at least one form of tramadol while maintaining bioavailability substantially equivalent to that of the immediate release composition.

In accordance with another aspect of the present invention, there is  
20 provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in combination with at least one pharmaceutically acceptable excipient, wherein the  
25 pharmaceutical composition when orally administered to a patient, produces a mean maximum plasma concentration ( $C_{max}$ ) of the at least one form of tramadol that is lower than that produced by an immediate release pharmaceutical composition of the at least one form of tramadol, and the area under the concentration-time curve (AUC) and the mean minimum plasma concentration  
30 ( $C_{min}$ ) are substantially equivalent to that of the immediate release pharmaceutical composition.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in combination with at least one pharmaceutically acceptable excipient, wherein the composition, when orally administered to a patient, produces a mean maximum plasma concentration ( $C_{max}$ ) of the at least one form of tramadol having both a maximum concentration ( $C_{max}$ ) and an area under a plasma concentration vs. time curve (AUC) within the range from about -20% to about +25% of that produced by an immediate release pharmaceutical composition of the at least one form of tramadol.

In an embodiment of the present invention, the at least one form of tramadol is tramadol hydrochloride and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20281, N75963, N75980, N75974, N76003, N75968, N75983, N76100, N75986, N75960, N75982, N75977, N75981, or N75962.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in combination with at least one pharmaceutically acceptable excipient, the composition exhibiting an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 0% up to about 30% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 5% to about 22% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 15% to about 38% (by weight) of the at least one form of tramadol is released, after 8 hours, more than about 40% (by weight) of the at least one form of tramadol is released.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in combination with at least one pharmaceutically acceptable excipient, the composition exhibiting an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 2% to about 10% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 12% to about 20% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 30% to about 38% (by weight) of the at least one form of tramadol is released, after 8 hours, from about 48% to about 56% (by weight) of the at least one form of tramadol is released, after 10 hours, from about 64% to about 72% (by weight) of the at least one form of tramadol is released, and after 12 hours, more than about 76% (by weight) of the at least one form of tramadol is released.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising:

- (i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof and at least one pharmaceutically acceptable excipient; and
- (ii) a coating comprising at least one water-insoluble, water-permeable film-forming polymer, at least one plasticizer and at least one water-soluble polymer.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition comprising:

- (i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof,

pharmaceutically acceptable salts thereof, and combinations thereof and at least one pharmaceutically acceptable excipient; and

- (ii) a coating comprising at least one water-insoluble, water-permeable film-forming polymer, at least one plasticizer and at least one water-soluble polymer, wherein the proportion of the at least one water-insoluble, water-permeable film-forming polymer varies from about 20% to about 90% of the coating dry weight, the proportion of the at least one plasticizer varies from about 5% to about 30% of the coating dry weight, and the proportion of the at least one water-soluble polymer varies from about 10% to about 75% of the coating dry weight.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising:

- (i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof and at least one pharmaceutically acceptable excipient; and

- (ii) a coating comprising at least one water-insoluble, water-permeable film-forming polymer, at least one plasticizer and at least one water-soluble polymer, wherein the composition exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 0% up to about 30% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 5% to about 22% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 15% to about 38% (by weight) of the at least one form of tramadol is released, and after 8 hours, more than about 40% (by weight) of the at least one form of tramadol is released.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising:

(i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof and at least one pharmaceutically acceptable excipient; and

5 (ii) a coating comprising at least one water-insoluble, water-permeable film-forming polymer, at least one plasticizer and at least one water-soluble polymer, wherein the composition exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 2% to about 10% (by weight) of the at least  
10 one form of tramadol is released, after 4 hours, from about 12% to about 20% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 30% to about 38% (by weight) of the at least one form of tramadol is released, after 8 hours, from about 48% to about 56% (by weight) of the at least one form of tramadol is released, after 10 hours, from about 64% to about 72% (by weight) of the  
15 the at least one form of tramadol is released, and after 12 hours, more than about 76% of the at least one form of tramadol is released.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising:

20 (i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof and at least one pharmaceutically acceptable excipient; and

(ii) a coating comprising at least one water-insoluble, water-permeable  
25 film-forming polymer, at least one plasticizer and at least one water-soluble polymer, wherein the proportion of the at least one water-insoluble, water-permeable film-forming polymer varies from about 20% to about 90% of the coating dry weight, the proportion of the at least one plasticizer varies from about 5% to about 30% of the coating dry weight, and the proportion of the at  
30 least one water-soluble polymer varies from about 10% to about 75% of the coating dry weight, and wherein the composition exhibits an *in vitro* dissolution

profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 0% up to about 30% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 5% to about 22% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 15% to about 38% (by weight) of the at least one form of tramadol is released, and after 8 hours, more than about 40% (by weight) of the at least one form of tramadol is released.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising:

- (i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof and at least one pharmaceutically acceptable excipient; and
- (ii) a coating comprising at least one water-insoluble, water-permeable film-forming polymer, at least one plasticizer and at least one water-soluble polymer, wherein the proportion of the at least one water-insoluble, water-permeable film-forming polymer varies from about 20% to about 90% of the coating dry weight, the proportion of the at least one plasticizer varies from about 5% to about 30% of the coating dry weight, and the proportion of the at least one water-soluble polymer varies from about 10% to about 75% of the coating dry weight, and wherein the composition exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37°C) such that after 2 hours, from about 2% to about 10% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 12% to about 20% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 30% to about 38% (by weight) of the at least one form of tramadol is released, after 8 hours, from about 48% to about 56% (by weight) of the at least one form of tramadol is released, after 10 hours, from about 64% to about 72% (by weight) of the at least one form of tramadol is released, and after 12 hours, more than about 76% (by weight) of the at least one form of tramadol is released.



In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in  
5 combination with at least one pharmaceutically acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, provides a mean maximum plasma concentration ( $C_{max}$ ) of the at least one form of tramadol from about 80 ng/ml to about 500 ng/ml.

10 In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in  
15 combination with at least one pharmaceutically acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, provides a time to mean peak plasma concentration ( $T_{max}$ ) of the at least one form of tramadol ranging from about 4 hours to about 14 hours.

In accordance with another aspect of the present invention, there is  
20 provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising at least one form of tramadol selected from the group consisting of tramadol, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, in combination with at least one pharmaceutically acceptable excipient, wherein the  
25 pharmaceutical composition, when administered to a patient, provides a plasma concentration time curve with an area under the curve (AUC) ranging from about 1000 ng.hr/ml to about 10000 ng.hr/ml.

In an embodiment of the present invention, the at least one form of tramadol is present in the pharmaceutical composition in an amount effective for  
30 the management of moderate to moderately severe pain.

In an embodiment of the present invention, the pharmaceutical composition comprises from about 25 mg to about 800 mg or more of the at least one form of tramadol.

5 In an embodiment of the present invention, the pharmaceutical composition comprises from about 50 mg to about 400 mg or more of the at least one form of tramadol.

In an embodiment of the present invention, the pharmaceutical composition comprises from about 100 mg to about 300 mg or more of the at least one form of tramadol.

10 In an embodiment of the present invention, the at least one form of tramadol is tramadol hydrochloride.

In an embodiment of the present invention, the core is in a form selected from the group consisting of a granule, a spheroid, a microsphere, a bead, a seed, a pellet, a microtablet, a tablet, a capsule, and combinations thereof.

15 In an embodiment of the present invention, the core is in the form of a tablet.

In an embodiment of the present invention, the modified release pharmaceutical composition is suitable for once daily dosing.

20 In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is selected from the group consisting of at least one release rate controlling pharmaceutically acceptable carrier, at least one diluent, at least one lubricant, at least one binder, at least one filler and combinations thereof.

25 In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is at least one diluent.

In an embodiment of the present invention, the at least one diluent is selected from the group consisting of lactose, microcrystalline cellulose, mannitol and combinations thereof.

30 In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is at least one lubricant.

In an embodiment of the present invention, the at least one lubricant is selected from the group consisting of stearic acid, magnesium stearate, glyceryl behenate, talc, sodium stearyl fumarate and combinations thereof.

5 In an embodiment of the present invention, the at least one lubricant is sodium stearyl fumarate.

In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is at least one binder.

10 In an embodiment of the present invention, the at least one binder is selected from the group consisting of modified starch, gelatin, polyvinylpyrrolidone, polyvinyl alcohol and combinations thereof.

In an embodiment of the present invention, the at least one binder is polyvinyl alcohol.

In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is at least one filler.

15 In an embodiment of the present invention, the at least one filler is selected from the group consisting of lactose, microcrystalline cellulose and combinations thereof.

In an embodiment of the present invention, the at least one filler is microcrystalline cellulose.

20 There are at least three types of modified release pharmaceutical compositions in the pharmaceutical art; namely those that are delayed release, those that are extended release, and those that are both delayed and extended release. Delayed release pharmaceutical compositions are often designed to prevent drug release in the upper part of the gastrointestinal tract. Modified  
25 release coatings used to prepare this type of pharmaceutical composition are commonly called enteric coatings in the pharmaceutical art. Extended release pharmaceutical compositions are designed to extend drug release over a period of time, a result which is often achieved by the application of a sustained or controlled release coating.

30 In an embodiment of the present invention, the modified release pharmaceutical composition is an extended release pharmaceutical composition.

In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is at least one release rate controlling pharmaceutically acceptable carrier.

5 In an embodiment of the present invention, the at least one release rate controlling pharmaceutically acceptable carrier may be incorporated into a matrix along with the at least one form of tramadol and/or may be applied as a release rate controlling coating.

10 In an embodiment of the present invention, the matrix is a normal release matrix having a coating which provides for modified release of the at least one form of tramadol.

In an embodiment of the present invention, the at least one release rate controlling pharmaceutically acceptable carrier is at least one sustained release pharmaceutically acceptable carrier.

15 In an embodiment of the present invention, the at least one sustained release pharmaceutically acceptable carrier is at least one solid sustained release pharmaceutically acceptable carrier.

In an embodiment of the present invention, the at least one solid sustained release pharmaceutically acceptable carrier is at least one solid sustained release pharmaceutically-acceptable polymer.

20 In an embodiment of the present invention, the at least one solid sustained release pharmaceutically-acceptable polymer is selected from the group consisting of at least one hydrophilic water-soluble polymer, at least one hydrophobic water-insoluble polymer and combinations thereof.

25 In an embodiment of the present invention, the modified release coating is semi-permeable.

In an embodiment of the present invention, the modified release coating comprises at least one water-insoluble, water-permeable film-forming polymer.

In an embodiment of the present invention, the at least one water-insoluble, water-permeable film-forming polymer is ethylcellulose.

30 In an embodiment of the present invention, the modified release coating further comprises at least one water-soluble polymer.

In an embodiment of the present invention, the at least one water-soluble polymer is polyvinylpyrrolidone.

In an embodiment of the present invention, the modified release coating further comprises at least one plasticizer.

5 In an embodiment of the present invention, the at least one plasticizer is dibutyl sebacate.

In an embodiment of the present invention, the at least one water-insoluble, water-permeable film-forming polymer is ethylcellulose, the at least one water-soluble polymer is polyvinylpyrrolidone and the at least one  
10 plasticizer is dibutyl sebacate.

In an embodiment of the present invention, the modified release pharmaceutical composition is in the form of a tablet.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition comprising:

15 (i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, polyvinyl alcohol, silicon dioxide and sodium stearyl fumarate; and

(ii) a coating comprising ethylcellulose, polyvinylpyrrolidone and  
20 dibutyl sebacate, wherein the proportion of ethylcellulose varies between about 20% and about 90% of the coating dry weight, the proportion of dibutyl sebacate varies between about 5% and about 30% of the coating dry weight, and the proportion of polyvinylpyrrolidone varies between about 10% and about 75% of the coating dry weight, and wherein the composition exhibits an *in vitro*  
25 dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 0% up to about 30% of the at least one form of tramadol is released, after 4 hours, from about 5% to about 22% of the at least one form of tramadol is released, after 6 hours, from about 15% to about 38% of the at least one form of tramadol is released, after 8 hours,  
30 more than about 40% of the at least one form of tramadol is released.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition comprising:

(i) a core comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, polyvinyl alcohol, silicon dioxide and sodium stearyl fumarate; and

(ii) a coating comprising ethylcellulose, polyvinylpyrrolidone and dibutyl sebacate, wherein the proportion of ethylcellulose varies between about 20% and about 90% of the coating dry weight, the proportion of dibutyl sebacate varies between about 5% and about 30% of the coating dry weight, and the proportion of polyvinylpyrrolidone varies between about 10% and about 75% of the coating dry weight, and wherein the composition exhibits an *in vitro* dissolution profile (measured using the USP Basket Method at 75 rpm in 900 ml 0.1 N HCl at 37 °C) such that after 2 hours, from about 2% to about 10% of the at least one form of tramadol is released, after 4 hours, from about 12% to about 20% of the at least one form of tramadol is released, after 6 hours, from about 30% to about 38% of the at least one form of tramadol is released, after 8 hours, from about 48% to about 56% of the at least one form of tramadol is released, after 10 hours, from about 64% to about 72% of the at least one form of tramadol is released, and after 12 hours, more than about 76% of the at least one form of tramadol is released.

In an embodiment of the present invention, the pharmaceutical composition is further coated with an immediate release coating comprising at least one form of tramadol.

## BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be further understood from the following description with references to the drawings in which:

Figure 1 compares the *in vitro* dissolution profiles of 100 mg Tramadol HCl ER Tablets formulated according to Lot Nos. 2159, 2162 and 2165.

Figure 2 illustrates the mean plasma Tramadol concentrations (ng/ml) over time following once a day Tramadol HCl ER Tablet (100 mg x 2) formulated according to Lot Nos. 2159, 2162 and 2165 vs Ultram® (50 mg x 2) q.i.d.

Figure 3 illustrates the mean plasma Desmethyltramadol concentrations (ng/ml) following once a day Tramadol HCl ER Tablet (100 mg x 2) formulated according to Lot Nos. 2159, 2162 and 2165 vs Ultram® (50 mg x 2) q.i.d.

Figure 4 illustrates the mean plasma Tramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

Figure 5 illustrates the mean plasma Tramadol concentrations on Day 5 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

Figure 6 illustrates the mean plasma Desmethyltramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

Figure 7 illustrates the mean plasma Desmethyltramadol concentrations on Day 5 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

Figure 8 illustrates the mean plasma Tramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 9 illustrates the mean plasma Tramadol concentrations on Day 5 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 10 illustrates the mean plasma Desmethyltramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 11 illustrates the mean plasma Desmethyltramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 12 illustrates the *in vitro* dissolution profiles of Tramadol HCl 100 mg ER Tablets formulated according to Lot Nos. 1-4.

Figure 13 illustrates the *in vitro* dissolution profile of a 200 mg Tramadol HCl ER Tablet formulated according to Example 4.

5        Figure 14 illustrates the *in vitro* dissolution profiles of 200 mg Tramadol HCl ER Tablets formulated according to Lot Nos. 5 to 7.

Figure 15 illustrates the comparison of the mean tramadol plasma concentration-time profiles resulting from the oral administration of Tramadol HCl 100 mg ER tablets (2 x 100 mg once a day) and Tramadol HCl 200 mg ER  
10       tablets (1 x 200 mg once a day) formulated according to an embodiment of the present invention.

Figure 16 illustrates the comparison of the mean M1 plasma concentration-time profiles resulting from the oral administration of Tramadol HCl 100 mg ER tablets (2 x 100 mg once a day) and Tramadol HCl 200 mg ER  
15       tablets (1 x 200 mg once a day) formulated according to an embodiment of the present invention.

Figure 17 illustrates the mean plasma Tramadol concentrations (ng/ml) over time after two 100 mg Tramadol HCl ER Tablets formulated according to an embodiment of the present invention or after one 200 mg Tramadol HCl ER  
20       Tablet formulated according to an embodiment of the present invention following a 10 hour overnight fast.

Figure 18 illustrates the mean plasma M1 concentrations (ng/ml) over time after two 100 mg Tramadol HCl ER Tablets formulated according to an embodiment of the present invention or after one 200 mg Tramadol HCl ER  
25       Tablet formulated according to an embodiment of the present invention following a 10 hour overnight fast.

Figure 19 illustrates the mean plasma M5 concentrations (ng/ml) over time after two 100 mg Tramadol HCl ER Tablets formulated according to an embodiment of the present invention or after one 200 mg Tramadol HCl ER  
30       Tablet formulated according to an embodiment of the present invention following a 10 hour overnight fast.



Figure 20 illustrates the mean plasma Tramadol concentrations (ng/ml) over time after a single dose of one 200 mg Tramadol HCl ER Tablet formulated according to an embodiment of the present invention under fasting or fed conditions.

5        Figure 21 illustrates the mean plasma M1 concentrations (ng/ml) over time after a single dose of one 200 mg Tramadol HCl ER Tablet formulated according to an embodiment of the present invention under fasting or fed conditions.

10       Figure 22 illustrates the mean plasma M5 concentrations (ng/ml) over time after a single dose of one 200 mg Tramadol HCl ER Tablet formulated according to an embodiment of the present invention under fasting or fed conditions.

15       Figure 23 compares the LS mean change from baseline to average of weeks 1-12 in arthritis pain intensity VAS scores (primary variables) for Tramadol HCl ER Tablets and placebo.

Figure 24 compares the LS mean change from baseline to different study time points in arthritis pain intensity VAS scores (primary variables) for Tramadol HCl ER Tablets and placebo.

20       Figure 25 compares the LS mean changes from baseline to Week 12 for the Tramadol HCl ER Tablets and placebo for each of the secondary variables.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

25       The present invention consists of a controlled release pharmaceutical composition, in one, embodiment a tablet, comprising at least one form of tramadol, wherein the pharmaceutical composition comprises a core and a coating.

30       The core comprises at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof, in one embodiment tramadol hydrochloride; and at least one pharmaceutically acceptable excipient, in one embodiment a lubricant, a binder and/or a filler, and optionally a glidant as well as other pharmaceutically acceptable excipients.

The at least one form of tramadol used in the present invention may be any form of tramadol conventional in the pharmaceutical art. The at least one form of tramadol used in the present invention may be tramadol. The at least one form of tramadol used in the present invention may be the individually  
5 optically active enantiomers of tramadol, such as for example, (+)-tramadol and (-)-tramadol. The at least one form of tramadol used in the present may be pharmaceutically acceptable salts of tramadol. Suitable pharmaceutically acceptable salts of tramadol for use as the at least one form of tramadol according to the present invention are those conventionally known in the art such as, for  
10 example, pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable acid addition salts of tramadol for use as the at least one form of tramadol according to the present invention may be the hydrochloride salt, the hydrobromide salt, the hydroiodide salt, the saccharinate salt etc. In one embodiment, the at least one form of tramadol is tramadol  
15 hydrochloride.

The at least one lubricant used in the present invention may be any lubricant conventional in the pharmaceutical art. The at least one lubricant used in the present invention may be stearic acid, magnesium stearate, glyceryl behenate, talc, mineral oil (in PEG), sodium stearyl fumarate, etc. In one  
20 embodiment, the at least one lubricant is sodium stearyl fumarate.

The at least one binder used in the present invention may be any binder conventional in the pharmaceutical art. The at least one binder used in the present invention may be a water-soluble polymer, such as modified starch, gelatin, polyvinylpyrrolidone, polyvinyl alcohol, etc. In one embodiment, the at  
25 least one binder is polyvinyl alcohol.

The at least one filler used in the present invention may be any filler conventional in the pharmaceutical art. The at least one filler used in the present invention may be lactose, microcrystalline cellulose, etc. In one embodiment, the  
at least one filler is microcrystalline cellulose.

30 The at least one glidant used in the present invention may be any glidant conventional in the pharmaceutical art. In one embodiment, the at least one

glidant is colloidal silicon dioxide. The colloidal silicon dioxide may suitably be, for example, AEROSIL® as supplied by Degussa. Similar colloidal silicon dioxides are also available from other suppliers. Preferably, the colloidal silicon dioxide used is AEROSIL® 200.

- 5       The above binders, lubricants, fillers, glidants, and any other pharmaceutically acceptable excipient that may be present can further be found in the relevant literature, for example in the *Handbook of Pharmaceutical Additives: An International Guide to More Than 6000 Products by Trade Name, Chemical, Function, and Manufacturer*; Michael and Irene Ash (Eds.); Gower Publishing Ltd.;  
10   Aldershot, Hampshire, England, 1995.

- The relative amounts of ingredients in the core are preferably as follows. The proportion of the at least one form of tramadol in the core may vary between about 70% and about 98% of the core dry weight. The proportion of the at least one lubricant in the core may vary between about 0.5% and about 10% of the core  
15   dry weight. The proportion of the at least one binder or at least one filler in the core may vary between about 1% and about 25% of the core dry weight.

- The manufacturing process of the core can be as follows. The at least one form of tramadol is first granulated with the at least one binder, in one embodiment a granulator, but not necessarily a fluidized bed granulator. The at  
20   least one binder is first dissolved or dispersed in a suitable solvent, in one embodiment water. The solution or suspension of the at least one binder is then sprayed onto the at least one form of tramadol in a granulator, in one embodiment a fluidized bed granulator. For example, fluidized bed granulators manufactured by Glatt (Germany) or Aeromatic (Switzerland) can be used for  
25   this operation. An alternative process can be to use a conventional or high shear mixer to proceed granulation. If necessary, the at least one form of tramadol can be mixed with a filler, prior to the granulation step. Granules once dried can be mixed with the other pharmaceutically acceptable excipients, especially with the at least one lubricant, but also with at least one glidant and any other  
30   pharmaceutically acceptable excipient suitable to improve processing. The mixture of granules (in one embodiment with the at least one lubricant), and

optionally at least one glidant is pressed into tablets. Alternatively, the at least one form of tramadol and the at least one lubricant can be mixed in a granulator, in one embodiment a fluidized bed granulator, and heated to the melting point of the at least one lubricant to form granules. This mixture can then be mixed with  
5 at least one suitable filler and compressed into tablets. Also, it is possible to mix the at least one form of tramadol and the at least one lubricant (in one embodiment polyvinyl alcohol) in a granulator, in one embodiment a fluidized bed granulator, and then to press the resulting granules into tablets. Tablets can be obtained by standard techniques, in one embodiment on a (rotary) press (for  
10 example Manesty Betapress®) fitted with suitable punches. The resulting tablets are hereinafter referred as tablet cores.

These tablet cores are then coated with the semi-permeable coating designed to achieve a controlled release of the at least one form of tramadol.

The coating comprises at least one water-insoluble, water-permeable film-forming polymer, together with at least one plasticizer and at least one water-soluble polymer.  
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The at least one water-insoluble, water-permeable film-forming polymer used in the present invention, may be any water-insoluble, water-permeable film-forming polymer conventional in the pharmaceutical art. The at least one  
20 water-insoluble, water-permeable film-forming polymer used in the present invention may be a cellulose ether, such as ethylcellulose, a cellulose ester, such as cellulose acetate, polyvinyl alcohol, etc. In one embodiment, the at least one water-insoluble, water-permeable film-forming polymer is ethylcellulose. The ethylcellulose may suitably be, for example, ETHOCEL® as supplied by Dow  
25 Chemical Company. Similar ethylcelluloses are also available from other suppliers. Preferably, the ethylcellulose used is ETHOCEL® PR, more preferably ETHOCEL® PR100.

The at least one plasticizer used in the present invention, may be any plasticizer conventional in the pharmaceutical art. The at least one plasticizer  
30 used in the present invention may be an ester such as a citrate ester, an oil such as castor oil, a polyalkylene glycol of various molecular weights, such as

polyethylene glycol. In one embodiment, the at least one plasticizer is dibutyl sebacate.

The at least one water-soluble polymer used in the present invention, may be any water-soluble polymer conventional in the pharmaceutical art. In one  
5 embodiment, the at least one water-soluble is polyvinylpyrrolidone. The polyvinylpyrrolidone may suitably be, for example, KOLLIDON® as supplied by BASF AG. Similar polyvinylpyrrolidones are also available from other suppliers. Preferably, the polyvinylpyrrolidone used is KOLLIDON® 90F.

Other pharmaceutically acceptable excipients can be used in the coating,  
10 such as for example, acrylic acid derivatives (available from Röhm Pharma under the trade name EUDRAGIT®), pigments, etc.

The relative amounts of ingredients in the coating are preferably as follows. The proportion of the at least one water-insoluble, water-permeable polymer (in one embodiment ethylcellulose) in the coating may vary between  
15 about 20% and about 90% of the coating dry weight. The proportion of the at least one water-soluble polymer (in one embodiment polyvinylpyrrolidone) in the coating may vary between about 10% and about 75% of the coating dry weight. The proportion of the at least one plasticizer (in one embodiment dibutyl sebacate) in the coating may vary between about 5% and about 30% of the  
20 coating dry weight. The relative proportions of ingredients, notably the ratio of the at least one water-insoluble, water-permeable film-forming polymer to the at least one water-soluble polymer, can be varied depending on the desired release profile (where a more delayed release is desired, it is generally obtained with a higher amount of the at least one water-insoluble, water-permeable film-forming  
25 polymer).

The coating process can be as follows. Ethylcellulose, dibutyl sebacate and polyvinylpyrrolidone are dissolved in a solvent such as denatured alcohol using a propeller stirrer until complete dissolution is achieved. The resulting solution is sprayed onto the tablet cores, using a perforated coating pan.

30 The weight ratio coating/tablet core is comprised e.g. between about 1/30 and about 3/10, preferably about 1/10.

The tablet comprises an amount of the at least one form of tramadol of from about 25 mg to about 800 mg or more per tablet.

The present invention thus provides a controlled release pharmaceutical composition comprising at least one form of tramadol selected from the group consisting of tramadol, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof, the composition exhibiting a dissolution profile such that after 2 hours, from about 0% up to about 30% (by weight) of the at least one form of tramadol is released, after 4 hours, from about 5% to about 22% (by weight) of the at least one form of tramadol is released, after 6 hours, from about 15% to about 38% (by weight) of the at least one form of tramadol is released, after 8 hours, more than about 40% (by weight) of the at least one form of tramadol is released.

In an embodiment of the present invention, the controlled release pharmaceutical composition is an extended release tablet, the tablet comprising:

- (i) a core comprising tramadol hydrochloride, polyvinyl alcohol, colloidal silicon dioxide and sodium stearyl fumarate; and
- (ii) a coating comprising ethylcellulose, polyvinylpyrrolidone and dibutyl sebacate.

Further details of the preferred embodiments of the present invention are illustrated in the following examples which are understood to be non-limiting.

**EXAMPLE 1:** 100 mg Tramadol HCl ER Tablets

The following 100 mg Tramadol HCl ER Tablet formulations were prepared:

**Table 1a:** Tablet Core Formulation

Ingredients	Quantity (mg)	%
Tramadol HCl	100.00	96.15
Polyvinyl Alcohol	2.00	1.92
Colloidal Silicon Dioxide (AEROSIL® 200)	1.00	0.96
Sodium Stearyl Fumarate	1.00	0.96
Purified Water	41.60 *	
<b>Core Total Weight</b>	<b>104.00</b>	<b>99.99</b>

\* evaporated during process

### Tablet Core Preparation

Tramadol HCl and colloidal silicon dioxide were mixed and passed through a 1.0 mm screen. Polyvinyl alcohol was dissolved in purified water. The mixed tramadol HCl and colloidal silicon dioxide powder was granulated with the aqueous solution of polyvinyl alcohol in a fluidized bed granulator, Glatt GPCG1 and then dried. After granulation, the granules were blended with sodium stearyl fumarate and then passed through a 1.0 mm screen. The blend was then compressed into tablet cores using a Manesty Betapress.

Table 1b: Coating Formulation

	mg/tablet		
	Lot#2159	Lot#2162	Lot#2165
Ingredients	Quantity (mg)	Quantity (mg)	Quantity (mg)
Ethylcellulose (ETHOCEL® PR 100)	9.20	9.81	9.54
Polyvinylpyrrolidone (KOLLIDON® 90F)	4.14	3.53	3.80
Dibutyl Sebacate	2.66	2.66	2.66
Denatured Alcohol	170.00 *	170.00 *	170.00 *

\* evaporated during process

### Coating Preparation

The ethyl alcohol and isopropanol were weighed and mixed. Dibutyl sebacate and ethylcellulose were added to and dissolved in the ethyl alcohol and isopropyl alcohol while stirring using a propeller stirrer, Coframo RZR1. The ethylcellulose and dibutyl sebacate were allowed to dissolve completely. The polyvinylpyrrolidone was added. The solution was stirred until all components were dissolved. The solution was passed through a high pressure homogenizer, Mini DeBee 2000 with #7 nozzle, Bee International. The tablet cores were coated using the coating solution in a perforated coating pan, O'Hara Labcoat III 36" Pan, Vector LCDS.

### Coating Parameters

Inlet Temperature:	48.5-49.5 °C
Outlet Temperature:	38.5-39.5 °C
Bed Temperature:	37.5-38.5 °C
Spray Rate:	300 g/min

Atomizing Air/Pattern: 25/25 psi  
Distance gun/Bed: 6"  
Distance between guns: 6"  
Pan speed: 12.0 rpm

5 Coating Amount

Diameter: 6 mm  
Thickness: 4.65 mm  
Cup Height: 1.02 mm  
Surface: 112 mm<sup>2</sup>

10 Percentage: 100 %  
Amount: 16 mg

Dissolution Method

*In vitro* dissolution studies were conducted on 100 mg Tramadol HCl ER Tablets formulated according to Lot#2159, Lot#2162 and Lot#2165. The following dissolution conditions were used for all of the *in vitro* dissolution studies conducted herein for determining the *in vitro* dissolution profiles of Tramadol HCl ER Tablets:

Apparatus: USP Basket (10 mesh)  
Dissolution medium: 0.1 N HCl  
20 Volume (vessels): 900 ml  
Bath temperature: 37°C (± 0.5°C)  
Wavelength: 271 nm  
Flow cell thickness: 1 cm  
Rotation speed: 75 rpm  
25 Total run time: 900 min  
Sampling interval: 30 min



Table 2: Dissolution Profile

Time (min.)	% Dissolved		
	Lot#2159	Lot#2162	Lot#2165
0	0	0	0
30	1.1	0.1	0.3
60	5.7	0.3	2.0
90	12.8	1.4	5.1
120	21.3	2.9	9.1
180	41.6	7.0	19.8
240	62.4	12.8	33.4
300	77.8	20.2	48.7
360	87.3	29.4	62.7
420	92.6	40.3	73.5
480	95.9	50.8	81.7
540	97.5	59.9	87.2
600	98.7	67.6	91.1
660	99.2	73.7	94.1
720	99.6	78.2	96.0
780	99.9	81.9	97.2
840		84.9	97.8
900		86.9	98.5
960		88.5	99.0

Figure 1 compares the *in vitro* dissolution profiles of 100 mg Tramadol HCl ER Tablets formulated according to Lot Nos. 2159, 2162 and 2165.

5 **Study No. 401 (B99-401PK-TRAP03)**

A pilot four-way, single-dose, open-label, fasting, comparative bioavailability study of three formulations of Tramadol Hydrochloride Extended-Release Tablets (2x100 mg) Versus Ultram® Tablets (50 mg q.i.d) in normal, healthy, Non-smoking male volunteers was conducted.

10 This pilot study evaluated the bioavailability of three novel Tramadol HCl Extended-Release Tablets (2x100 mg) against Ultram® (Ortho-McNeil Pharmaceuticals) Tablets (50 mg q.i.d.) under fasting conditions.

This pilot study was a randomized, balanced, four-period, four-treatment, four-sequence crossover study design in sixteen (16) normal, healthy, non-smoking male volunteers and two (2) alternates.

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Eighteen (18) subjects were entered into the study. Fourteen (14) subjects completed the study; there were fourteen (14) evaluable subjects. All subjects were non-smoking, between 18 and 45 years of age (inclusive), and with body weights no more than  $\pm 15\%$  of the ideal weight for the subject's height and frame as determined by the Table of Desirable Weights for Men and Women.

The study periods were separated by a one-week washout period. Blood sampling for drug content analysis was carried out at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-drug when each test drug was administered. Blood sampling for drug content analysis was carried out at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0 (pre-drug), 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 (pre-drug), 12.0, 13.0, 14.0, 15.0 (pre-drug), 16.0, 17.0, 18.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-drug when the reference drug was administered.

Treatments: A: Tramadol HCl ER 200 mg Tablets  
Lot Number: 2159

B: Tramadol HCl ER 200 mg Tablets  
Lot Number: 2162

C: Tramadol HCl ER 200 mg Tablets  
Lot Number: 2165

D: Ultram® 50 mg Tablets  
Control Number: CDA 2225; Expiry Date: 4/01  
(Ortho-McNeil Pharmaceuticals, U.S.A.)

The three 100 mg extended release tramadol formulations tested (2x100 once a day) demonstrated prolonged tramadol and mono-O-desmethyltramadol plasma concentration-time profiles relative to the Ultram® tablet (1 x 50mg) when administered 4 times a day (2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> doses at 5, 11 and 15 hours post-1<sup>st</sup> dose, respectively) (See figures 2 and 3). In addition, the ER formulations yielded equivalent AUCs relative to an equivalent dose of the Ultram® immediate release tablet. The 90% geometric mean confidence intervals for AUC<sub>t</sub> and AUC<sub>∞</sub> were within the 80%-125% range for all three test formulations. Formulations 2162 and 2165 also yielded equivalent C<sub>max</sub> values versus Ultram® as evidenced by 90% geometric confidence intervals within the 80-125% range. The mean pharmacokinetic parameters and 90% confidence interval for ratio of the

geometric mean AUC and  $C_{max}$  are presented in Tables 3a and 3b for tramadol and in Tables 4a and 4b for O-desmethyltramadol. Table 3a also shows that overall there was no apparent difference in the ratio of metabolite ( $AUC_{\infty}$  of M1/tramadol) among the ER tramadol formulations and the immediate release tablet. The half-life following Ultram® treatment was slightly shorter compared to the extended release formulations.

**Table 3a: Pharmacokinetic Parameters Study 401PK (n = 14)**

**Study 401PK Mean Pharmacokinetic Parameters for Plasma Tramadol (n = 14)**

Parameter	Lot# 2159 1x200mg	Lot# 2162 1x200mg	Lot# 2165 1x200mg	Ultram 50mg q.i.d
	Mean (CV %)	Mean (CV %)	Mean (CV %)	Mean (CV %)
AUC <sub>t</sub> (hr*ng/mL)	4796.83 (42.92)	4663.89 (34.42)	4827.94 (44.08)	4915.71 (43.81)
AUC <sub>∞</sub> (hr*ng/mL)	4936.23 (45.71)	4897.97 (38.96)	5028.36 (46.36)	5118.72 (47.88)
C <sub>max</sub> (ng/mL)	351.60 (28.89)	246.46 (32.13)	298.30 (38.34)	284.70 (36.17)
T <sub>max</sub> (hr)	5.86 (21.02)	9.86 (21.74)	8.43(19.03)	14.07 (37.03)
Half-life (hr)	6.90 (32.10)	7.94 (32.96)	7.49 (37.02)	6.73 (37.46)
M1/Tramadol	0.29 (50.96)	0.30 (45.62)	0.29 (49.35)	0.29 (52.92)
MRT (hr)	13.70 (24.08)	19.48 (18.19)	16.57 (22.61)	17.79 (19.03)
Lag Time (hr)	0.00 (0.00)	1.00 (0.00)	0.64 (77.35)	0.00 (0.00)

Figure 2 illustrates the mean plasma Tramadol concentrations (ng/ml) over time following once a day Tramadol HCl ER Tablet (100 mg x 2) formulated according to Lot Nos. 2159, 2162 and 2165 vs Ultram® (50 mg x 2) q.i.d.

**Table 3b: Ratio of Means & 90% Confidence Interval for Plasma Tramadol**

	AUC(0-t)			AUC(0-∞)			C <sub>max</sub>		
	90% CI	Ratio of Means	CV(%)	90% CI	Ratio of Means	CV(%)	90% CI	Ratio of Means	CV(%)
Formulation A (Lot # 2159)	90.1 - 105.1	97.3	11.5	89.2 - 104.4	96.5	11.7	114.2 - 140.0	126.5	15.2
Formulation B (Lot # 2162)	93.1 - 109.6	101	11.5	93.7 - 110.7	101.9	11.7	80.5 - 101.1	90.7	15.2
Formulation C (Lot # 2165)	94.0 - 109.6	101.5	11.5	94.0 - 110.1	101.7	11.7	99.0 - 121.4	109.6	15.2

**Table 4a: Pharmacokinetic Parameters Study 401 (401PK) (n = 14)**

**Study 401PK: Mean Pharmacokinetic Parameters for Plasma O-desmethyltramadol (n=12)**

Parameter	Lot# 2159 1x200mg	Lot# 2162 1x200mg	Lot# 2165 1x200mg	Ultram 50mg q.i.d
	Mean (CV %)	Mean (CV %)	Mean (CV %)	Mean (CV %)
AUC <sub>t</sub> (hr*ng/mL)	1193.78 (44.84)	1230.54 (40.02)	1169.03 (39.15)	1166.74 (33.21)
AUC <sub>∞</sub> (hr*ng/mL)	1226.20 (44.26)	1295.76 (41.06)	1218.22 (39.68)	1201.62 (32.42)
C <sub>max</sub> (ng/mL)	68.91 (39.65)	56.49 (36.64)	61.75 (39.92)	60.72 (35.05)
T <sub>max</sub> (hr)	7.29 (23.11)	13.29 (21.78)	10.14 (29.41)	16.71 (4.35)
Half-life (hr)	7.56 (30.98)	8.80 (36.96)	8.16 (28.65)	7.50 (32.79)

- 5 Figure 3 illustrates the mean plasma Desmethytramadol concentrations (ng/ml) following once a day Tramadol HCl ER Tablet (100 mg x 2) formulated according to Lot Nos. 2159, 2162 and 2165 vs Ultram® (50 mg x 2) q.i.d.

**Table 4b: Ratio of Means & 90% Confidence Interval for Plasma O-desmethytramadol**

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	AUC(0-t)		AUC(0-∞)		C <sub>max</sub>	
	90% CI	Ratio of Means	90% CI	Ratio of Means	90% CI	Ratio of Means
Formulation A (Lot # 2159)	87.8 - 109.7	98.1	87.6 - 108.9	97.7	98.3 - 124.6	110.7
Formulation B (Lot # 2162)	91.0 - 115.2	102.4	93.0 - 117.1	104.3	80.7 - 103.7	91.4
Formulation C (Lot # 2165)	89.0 - 111.2	99.5	89.7 - 111.6	100.1	89.4 - 113.3	100.7

**Study No. 99103 (B99-416PK-TRAP03)**

- 15 A pilot two-way, multiple-dose, open-label, Fasting, comparative bioavailability study of Tramadol Hydrochloride Extended-Release Tablets (2x100 mg) versus Ultram® in normal, healthy, non-smoking male and female volunteers was conducted.

20 The objective of this study was to compare the rate and extent of absorption of a new extended-release formulation of tramadol hydrochloride (2x100 mg) against Ultram® (50 mg q.i.d.) under steady-state conditions in normal healthy male and female volunteers. This comparison reflects the administration of Ultram® under clinical conditions.

This pilot steady-state study was a randomized, two-way crossover study design in sixteen (16) normal, healthy, non-smoking male and female volunteers and four (4) alternates (total 11 males and 9 females).

Twenty (20) subjects were entered into the study. Fifteen (15) subjects  
5 completed the study; there were fifteen (15) evaluable subjects. All subjects were non-smoking, between 18 and 45 years of age (inclusive), and with body weights no more than  $\pm 15\%$  of the ideal weight for the subject's height and frame as determined by the Table of Desirable Weights for Men and Women. All female subjects were non-lactating, had negative pregnancy tests, and were taking an  
10 acceptable method of contraception.

The study periods were separated by a one-week washout period. Blood sampling for drug content analysis was carried out as follows for the test product (Tramadol ER tablets (2x100 mg), treatment A, Lot# 2162): Day 1 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0; Day 2, 3, and 4 - 0.0 (pre-dose);  
15 Day 5 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-drug administration.

Blood sampling for drug content analysis was carried out as follows for the reference product (Ultram® 50 mg tablets q.i.d., treatment B, Lot# CDA2225):  
Day 1 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0 (pre-dose), 6.0, 7.0, 8.0, 9.0, 10.0, 11.0  
20 (pre-dose), 12.0, 13.0, 14.0, 15.0 (pre-dose), 16.0, 17.0, 18.0, 20.0 and 24.0; Days 2, 3, and 4 - 0.0 (pre-dose); Day 5 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0 (pre-dose), 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 (pre-dose), 12.0, 13.0, 14.0, 15.0 (pre-dose), 16.0, 17.0, 18.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-drug administration.

Treatments: A: 2 Tablets of Tramadol HCl ER 100 mg Tablets (Lot# 2162 -  
25 Biovail Corporation International, Canada) once a day (approximately 7 AM) for 5 consecutive days.

B: Ultram® (Tramadol HCl 50 mg tablet, Ortho-McNeil  
30 Pharmaceutical, USA) (Lot# CDA2225) q.i.d. (approximately 7 AM, 12 PM, 6 PM and 10 PM) for 5 consecutive days.

In the current study, Lot# 2162 was compared to immediate release Ultram® under multiple-dose conditions. The extended release formulation

performed consistently under both single and multiple doses. The overall half-life after multiple-dose for tramadol was 7.3 hours and 6.7 hours, respectively, following Tramadol HCl ER Tablets and Ultram®. Steady state levels of tramadol were achieved by the third dose (day 3 of the study) for Tramadol HCl ER Tablets, and by the fifth dose (Day 2 of the study) for Ultram®. The mean pharmacokinetic data for single dose and multiple dose of tramadol and the M1 are presented in tables 5a - 5b and 6a - 6b, respectively. Steady-state bioequivalence between Tramadol HCl ER Tablets (Lot# 2162) and immediate-release Ultram® (Lot # CDA2225) was established. The 90% confidence intervals for AUC and  $C_{max}$  were within the 80-125% limits for both unchanged drug and O-desmethytramadol. Tramadol HCl ER Tablets (Lot# 2162) given once daily exhibited lower percent fluctuation at steady state (70%) than Ultram® given four times a day.

Table 5a: Pharmacokinetic Parameters Study 99103 (416PK) (n = 15)

Study 416PK Mean Pharmacokinetic Parameters for Plasma Tramadol (n = 15)

Parameter	Tramadol ER (2x100 mg) q.d.		Ultram 50 mg q.i.d.	
	Day 1	Day 5	Day 1	Day 5
AUC <sub>0-∞</sub> (ng hr/mL)	5089.010 (37.55)	7715.89 (35.69)	5000.73 (37.94)	7004.37 (27.81)
$C_{max}$ (ng/mL)	365.62 (40.34)	431.58 (34.06)	348.23 (36.73)	406.95 (26.88)
$T_{max}$ (hr)	13.47 (19.82)	12.80 (21.13)	16.00 (10.02)	15.80 (26.23)
$t_{1/2\ el}$ (hr)		7.32 (16.41)		6.67 (20.24)
% Fluctuation		70.19 (24.19)		81.82 (20.28)
$C_{min}$ (ng/mL)	Tramadol ER (2x100 mg) q.d.		Ultram 50 mg q.i.d.	
Day 1	161.37 (70.23)		147.52 (49.96)	
Day 2	213.43 (52.38)		178.52 (47.03)	
Day 3	235.13 (56.41)		183.89 (36.33)	
Day 4	231.44 (44.66)		176.41 (44.24)	
Day 5	253.55 (46.44)		201.20 (26.12)	

Figure 4 illustrates the mean plasma Tramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

- 5 Figure 5 illustrates the mean plasma Tramadol concentrations on Day 5 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

**Table 5b: Ratio of Means & 90% Confidence Interval for Plasma Tramadol**

Statistical Analysis (ANOVA)	Treatment	Ratio <sup>1</sup>	90 % Geometric C.I. <sup>2</sup>	
	Comparisons		Lower	Upper
AUC <sub>0-t</sub>	Tramadol HCl ER (Lot#2162) vs Ultram® (Lot# CDA2225)	108.6%	104.2%	113.2%
C <sub>max</sub>	Tramadol HCl ER (Lot#2162) vs Ultram® (Lot# CDA2225)	104.9%	98.6%	111.6%

<sup>1</sup>Ratio of least squares means

<sup>2</sup>Calculated from log-transformed data

Table 6a: Pharmacokinetic Parameters Study 99103 (416PK) (n = 15)

Study 416PK: Mean Pharmacokinetic Parameters for Plasma O-desmethyltramadol  
(n = 15)

Parameter	Tramadol ER (2x100 mg) q.d.		Ultram 50 mg q.i.d.	
	Day 1	Day 5	Day 1	Day 5
AUC <sub>0-∞</sub> (ng hr/mL)	1037.71 (40.22)	1550.55 (37.21)	1105.30 (37.74)	1540.17 (39.07)
C <sub>max</sub> (ng/mL)	70.85 (39.87)	79.75 (36.94)	72.82 (37.02)	80.97 (41.13)
T <sub>max</sub> (hr)	14.27 (21.76)	13.73 (16.39)	16.87 (8.34)	13.47 (41.43)
t <sub>1/2 el</sub> (hr)		8.49 (14.28)		7.15 (12.75)
% Fluctuation		49.46 (22.71)		55.08 (33.22)
C <sub>min</sub> (ng/mL)	Tramadol ER (2x100 mg) q.d.		Ultram 50 mg q.i.d.	
Day 1	40.05 (45.16)		41.34 (38.83)	
Day 2	54.73 (39.72)		49.41 (37.52)	
Day 3	56.67 (36.46)		50.03 (37.94)	
Day 4	56.55 (37.43)		47.35 (40.18)	
Day 5	55.19 (38.43)		50.86 (39.67)	

5 Figure 6 illustrates the mean plasma Desmethyltramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

Figure 7 illustrates the mean plasma Desmethyltramadol concentrations on Day 5 following once a day Tramadol HCl ER Tablets (100 mg x 2) formulated according to Lot# 2162 for 5 Days vs. Ultram® (50 mg x 2) q.i.d.

10



Table 6b: Ratio of Means & 90% Confidence Interval for Plasma O-desmethyltramadol

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio <sup>1</sup>	90 % Geometric C.I. <sup>2</sup>	
			Lower	Upper
AUC <sub>0-t</sub>	Tramadol HCl ER (Lot#2162) vs Ultram® (Lot# CDA2225)	101.5%	97.2%	106.0%
C <sub>max</sub>	Tramadol HCl ER (Lot#2162) vs Ultram® (Lot# CDA2225)	100.0%	94.2%	106.2%

<sup>1</sup>Ratio of least squares means

<sup>2</sup>Calculated from log-transformed data

#### 5 Study No. 2282 (B99-424PK-TRAP03)

A pilot three-way, multiple-dose, open-label, fasting, comparative bioavailability study of two formulations of Tramadol Hydrochloride Extended-Release Tablets (3x100 mg) administered once a day versus Ultram® Tablets (2x50 mg) administered three times a day in normal, healthy, non-smoking male and female volunteers was conducted.

The objective of this study was to compare the rate and extent of absorption of two new extended-release formulations of tramadol hydrochloride (3x100 mg) administered once daily against Ultram® (2x50 mg) administered three times a day under steady-state conditions in normal healthy male and female volunteers. This comparison reflects the administration of Ultram® under clinical conditions.

This pilot steady-state study was a randomized, three-way crossover study design in fifteen (15) normal, healthy, non-smoking male and female volunteers and three (3) alternates (total 11 males and 9 females). Eighteen (18) subjects were entered into the study. Fourteen (14) subjects completed the study; there were fourteen (14) evaluable subjects. All subjects were non-smoking, between 18 and 45 years of age (inclusive), and with body weights no more than ±15% of the ideal weight for the subject's height and frame as determined by the Table of Desirable Weights for Men and Women. All female subjects were non-

lactating, had negative pregnancy tests, and were taking an acceptable method of contraception.

The study periods were separated by a one-week washout period. Blood sampling for drug content analysis was carried out as follows for the two test products (Tramadol ER tablets (3x100 mg), treatment A (Lot# 2162) and treatment B (Lot# 2165)): Day 1 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, Day 2, 3, and 4 - 0.0 (pre-dose); Day 5 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0 and 48.0 hours post-drug administration.

Blood sampling for drug content analysis was carried out as follows for the reference product (Ultram® 50 mg tablets q.i.d., treatment C): Day 1 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0 (pre-dose), 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 (pre-dose), 12.0, 13.0, 14.0, 16.0, and 20.0 hours; Days 2, 3, and 4 - 0.0 (pre-dose); Day 5 - 0.0 (pre-dose), 1.0, 2.0, 3.0, 4.0, 5.0 (pre-dose), 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 (pre-dose), 12.0, 13.0, 14.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post-drug administration.

Treatments: A: 3 Tablets of Tramadol HCl ER 100 mg Tablets (Lot# 2162 - Biovail Corporation International, Canada) once a day (approximately 7 AM) for 5 consecutive days.

B: 3 Tablets of Tramadol HCl ER 100 mg Tablets (Lot# 2165 - Biovail Corporation International, Canada) once a day (approximately 7 AM) for 5 consecutive days.

C: 2 Tablets of Ultram® (Tramadol HCl 50 mg tablet, Ortho-McNeil Pharmaceutical, USA) (Lot# CDA2225) t.i.d. (approximately 7 AM, 12 PM and 6 PM) for 5 consecutive days.

The current study was undertaken to compare the two lead Tramadol HCl ER Tablet formulations (Lot# 2162 and Lot# 2165) (3x100 mg) administered once daily against Ultram® (2x50 mg) administered three times a day under steady-state conditions in normal healthy male and female volunteers. This comparison reflects the administration of Ultram® under clinical conditions.

The extended release formulations performed consistently both under single and multiple dose conditions. The overall half-life after multiple-dose for tramadol was 7.3 hours following Tramadol HCl ER Tablets (Lot# 2162), 6.9 hours following Tramadol HCl ER Tablets (Lot# 2165), and 6.4 hours immediate release Ultram®. Steady state levels of tramadol were achieved by the third dose (day 3 of the study) for Tramadol HCl ER Tablets, (Lot# 2162 and Lot# 2165) and by the seventh dose (day 3 of the study) for Ultram®. The mean pharmacokinetic data for single dose and multiple doses of tramadol and the M1 are presented in tables 7a - 7b and 8a - 8b, respectively. Steady-state bioequivalence between Tramadol HCl ER tablets (Lot# 2162 and Lot# 2165) and immediate-release Ultram® (Lot # CDA2225) was established. The 90% confidence intervals for unchanged drug and O-desmethyltramadol AUC and  $C_{max}$  for Tramadol HCl ER Tablets (Lot# 2162), and the 90% confidence intervals for unchanged drug and O-desmethyltramadol AUC for Tramadol HCl ER Tablets (Lot# 2165) were within the 80-125% limits. O-desmethyltramadol  $C_{max}$  for Lot# 2165 was within the limits.

Lot# 2162 demonstrates steady-state bioequivalence versus both t.i.d. and q.i.d. administration of Ultram® as evidenced by 90% C.I. values for AUC and  $C_{max}$  within 80-125% limits for both tramadol and O-desmethyltramadol. Lot# 2162 also exhibited lower percent fluctuation versus Ultram® when given t.i.d. and q.i.d.

Table 7a: Pharmacokinetic Parameters Study 2282 (424PK) (n = 15)

Study 424PK Mean Pharmacokinetic Parameters for Plasma Tramadol (n = 15)

Parameter	Tramadol ER (2x100 mg) q.d. Lot # 2162		Tramadol ER (2x100 mg) q.d. Lot # 2165		Ultram 50 mg q.i.d. Lot #	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
AUC <sub>0-8</sub> (ng hr/mL)	6407.95 (27.03)	9849.28 (23.65)	6977.91 (27.97)	10116.75 (23.97)	6854.57 (25.77)	9611.88 (19.12)
C <sub>max</sub> (ng/mL)	457.65 (28.37)	585.17 (21.58)	540.76 (24.05)	699.76 (22.32)	464.67 (23.46)	621.66 (20.06)
T <sub>max</sub> (hr)	10.40 (20.80)	10.90 (27.70)	7.90 (18.6)	8.40 (21.20)	12.20 (34.20)	9.60 (36.10)
t <sub>1/2 α</sub> (hr)		7.32 (23.58)		6.91 (17.33)		6.40 (14.20)
% Fluctuation		84.73 (36.04)		125.39 (24.96)		114.47 (15.79)
C <sub>min</sub> (ng/mL)	Tramadol ER (2x100 mg) q.d. Lot # 2162		Tramadol ER (2x100 mg) q.d. Lot # 2165		Ultram 50 mg q.i.d. Lot #	
	Day 2	Day 3	Day 4	Day 5	Day 2	Day 3
	174.56 (40.90)	213.73 (41.07)	218.78 (44.50)	250.77 (43.26)	142.63 (36.88)	154.99 (39.36)
			175.36 (46.91)	186.04 (47.41)	150.46 (32.52)	166.85 (31.67)

Table 7b: Ratio of Means &amp; 90% Confidence Interval for Plasma Tramadol

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio <sup>1</sup>	90 % Geometric C.I. <sup>2</sup>	
			Lower	Upper
AUC <sub>0-t</sub>	Tramadol ER (Lot#2162) vs Ultram® (Lot# CDA2225)	101.9%	95.4%	108.8%
	Tramadol ER (Lot# 2165) vs Ultram® (Lot# CDA2225)	104.9%	98.2%	112.0%
C <sub>max</sub>	Tramadol ER (Lot#2162) vs Ultram® (Lot# CDA2225)	93.1%	83.9%	103.4%
	Tramadol ER (Lot#2165) vs Ultram® (Lot# CDA2225)	114.1%	102.8%	126.7%

5 <sup>1</sup>Ratio of least squares means<sup>2</sup>Calculated from log-transformed data

**Table 8a: Pharmacokinetic Parameters Study 2282 (424PK) (n = 15)**

**Study 424PK: Mean Pharmacokinetic Parameters for Plasma O-desmethyltramadol (n = 15)**

Parameter	Tramadol ER (2x100 mg) q.d. Lot # 2162		Tramadol ER (2x100 mg) q.d. Lot # 2165		Ultram 50 mg q.i.d. Lot #	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
AUC <sub>0-t</sub> (ng hr/mL)	1896.02 (26.07)	2554.04 (26.68)	2133.71 (32.64)	2478.46 (32.46)	2096.32 (24.41)	2475.64 (25.10)
C <sub>max</sub> (ng/mL)	130.64 (30.58)	138.37 (24.02)	150.67 (33.05)	145.57 (29.10)	127.43 (24.32)	138.26 (26.73)
T <sub>max</sub> (hr)	11.60 (19.80)	12.60 (22.00)	9.60 (14.60)	9.20 (18.80)	13.20 (29.90)	13.20 (14.30)
C <sub>min</sub> (ng/mL)	Tramadol ER (2x100 mg) q.d.		Tramadol ER (2x100 mg) q.d.		Ultram 50 mg q.i.d.	
Day 2	64.24 (34.32)		52.92 (46.34)		57.74 (25.59)	
Day 3	70.48 (33.65)		55.29 (41.81)		56.61 (28.78)	
Day 4	76.09 (41.83)		60.05 (44.08)		57.67 (28.81)	
Day 5	76.87 (38.41)		59.65 (45.35)		58.82 (30.95)	

5 **Table 8b: Ratio of Means & 90% Confidence Interval for Plasma O-desmethyltramadol**

Statistical Analysis (ANOVA)	Treatment	Ratio <sup>1</sup>	90 % Geometric C.I. <sup>2</sup>	
	Comparisons		Lower	Upper
AUC <sub>0-t</sub>	Tramadol ER (Lot# 2162) vs Ultram® (Lot# CDA2225)	102.4%	96.9%	108.1%
	Tramadol ER (Lot# 2165) vs Ultram® (Lot# CDA2225)	98.6%	93.4%	104.2%
C <sub>max</sub>	Tramadol ER (Lot# 2162) vs Ultram® (Lot# CDA2225)	100.4%	95.0%	106.0%
	Tramadol ER (Lot# 2165) vs Ultram® (Lot# CDA2225)	105.3%	99.7%	111.3%

<sup>1</sup>Ratio of least squares means

<sup>2</sup>Calculated from log-transformed data

Figure 8 illustrates the mean plasma Tramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 9 illustrates the mean plasma Tramadol concentrations on Day 5 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 10 illustrates the mean plasma Desmethyltramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

Figure 11 illustrates the mean plasma Desmethyltramadol concentrations on Day 1 following once a day Tramadol HCl ER Tablets (100 mg x 3) formulated according to Lot Nos. 2162 and 2165 for 5 Days vs. Ultram® (50 mg x 2) t.i.d.

#### 10 EXAMPLE 2: 100 mg Tramadol HCl ER Tablets

The following 100 mg Tramadol HCl ER Tablet formulation was prepared:  
Tablet Core Formulation

The tablet core formulation was that of Example 1. The tablet core was prepared according to the process described in Example 1.

#### 15 Table 9: Coating Formulation

Ingredients	Quantity (mg)	%
Ethylcellulose (ETHOCEL® PR 100)	9.73	73.00 (of coating polymer)
Polyvinylpyrrolidone (KOLLIDON® 90F)	3.60	27.00 (of coating polymer)
Dibutyl Sebacate	2.67	20.00 (of above polymer)
<b>Total dry material: 8.5% of the solution</b>		
Ethyl Alcohol 200 Proof	163.62 *	95% (of total solvent)
Isopropyl Alcohol 99%	8.61 *	5% (of total solvent)
<b>Coated Tablet</b>	<b>120.00</b>	

\* evaporated during process

The coating process was carried out with the following parameters:

- 30 psi spray pressure
- 40°C product temperature
- 20 - 5 g/min/kg spray rate

#### EXAMPLE 3: 100 mg Tramadol HCl ER Tablets

The following 100 mg Tramadol HCl ER Tablet formulation was prepared:  
Tablet Core Formulation

The tablet core formulation was that of Example 1.

#### Tablet Core Preparation

The tablet core was prepared according to the process described in Example 1.

5 Table 10: Coating Formulation

Ingredients	mg/tablet			
	Lot#1	Lot#2	Lot#3	Lot#4
	Quantity (mg)	Quantity (mg)	Quantity (mg)	Quantity (mg)
Ethylcellulose (ETHOCEL® PR 100)	9.87	9.87	9.60	9.60
Polyvinylpyrrolidone (KOLLIDON® 90F)	3.47	3.47	3.73	3.73
Dibutyl Sebacate	2.67	2.67	2.67	2.67
Ethyl Alcohol 200 Proof	153.94 *	153.94 *	153.94 *	153.94 *
Isopropyl Alcohol 99% USP	8.09*	8.09*	8.09*	8.09*

\* evaporated during process

#### Coating Preparation

The tablet core coating solution was prepared according to the process described in Example 1.

10 Table 10: Coating Parameters:

Parameter	Lot #1	Lot#2	Lot #3	Lot #4
Inlet Temperature C°	41-42	56-57	56-57	48.5-49.5
Outlet Temperature C°	32-33	44-45	44-45	38.5-39.5
Bed Temperature C°	N/A	45-46	45-46	37.5-38.5
Spray Rate g/min	300	300-310	300-310	300
Atomizing Air/Pattern Psi	25/20	25/25	25/25	25/25
Distance gun/Bed	6"	6"	6"	6"
Distance between guns	6"	6"	6"	6"
Pan speed rpm	12.0	12.0	12.0	12.0

Table 11: Dissolution Profile

Time (min.)	% Dissolved			
	Lot #1	Lot#2	Lot #3	Lot #4
0	0	0	0	0
120	0.5	3.34	7.81	5.13
240	0.85	7.94	26.68	15.23
360	1.39	13.06	50.97	34.94
480	2.43	20.72	70.16	54.58
600	4.04	30.15	83.27	70.10
720	6.89	41.77	91.40	81.89

Figure 12 illustrates the *in vitro* dissolution profiles of Tramadol HCl 100 mg ER Tablets formulated according to Lot Nos. 1-4.

5 **EXAMPLE 4:** 200 mg Tramadol HCl ER Tablets

The following 200 mg Tramadol HCl ER Tablet formulation was prepared:

Table 12a: Tablet Core Formulation

Ingredients	Quantity (mg)
Tramadol HCl	200.00
Polyvinyl Alcohol	4.00
Colloidal Silicon Dioxide (AEROSIL® 200)	2.00
Sodium Stearyl Fumarate	2.00
Purified Water	83.20 *
<b>Core Total Weight</b>	<b>208.00</b>

\* evaporated during process

Tablet Core Preparation

- 10 The tablet core was prepared according to the process described in Example 1.

Table 12b: Coating Formulation

Ingredients	Quantity (mg)
Ethylcellulose (ETHOCEL® PR100)	12.28
Polyvinylpyrrolidone (KOLLIDON® K90)	6.05
Dibutyl Sebacate NF	3.67
Ethyl Alcohol 200 Proof	154.24 *
Isopropyl Alcohol USP	8.12 *

\* evaporated during process



### Coating Preparation

The tablet core coating solution was prepared according to the process described in Example 1.

Table 13: Dissolution Profile

Time (min.)	% Dissolved
0	0
60	1.13
120	6.05
180	13.80
240	22.87
300	32.18
360	41.17
420	49.43
480	56.85
540	63.33
600	68.87
660	73.55
720	77.55
780	80.72
840	83.43
900	85.77
960	87.75
1020	89.20
1080	90.70
1140	91.62

5

Figure 13 illustrates the *in vitro* dissolution profile of a 200 mg Tramadol HCl ER Tablet formulated according to Example 4.

### EXAMPLE 5: 200 mg Tramadol HCl Tablets

The following Tramadol HCl formulation was prepared:

#### 10 Tablet Core Formulation

The tablet core formulation was that of Example 4.

#### Tablet Core Preparation

The tablet core was prepared according to the process described in Example 1.

15

Table 14: Coating Formulation

Ingredients	Quantity (mg)	%
Ethylcellulose (ETHOCEL® PR 100)	13.38	73.00 (of coating polymer)
Polyvinylpyrrolidone (KOLLIDON® 90F)	4.95	27.00 (of coating polymer)
Dibutyl Sebacate	3.67	20.00 (of above polymer)
<b>Total dry material: 9% of the solution</b>		
Ethyl Alcohol 200 Proof	211.32 *	95% (of total solvent)
Isopropyl Alcohol 99%	11.12 *	5% (of total solvent)
<b>Coated Tablet</b>	<b>230.00</b>	

\* evaporated during process

The coating process was carried out with the following parameters:

- 30 psi spray pressure
- 5 - 40°C product temperature
- 5 g/min/kg spray rate

#### EXAMPLE 6: 200 mg Tramadol HCl ER Tablets

The following Tramadol HCl formulation was prepared:

#### Tablet Core Formulation

- 10 The tablet core formulation was that of Example 4.

#### Tablet Core Preparation

The tablet core was prepared according to the process described in Example 1.

Table 15: Coating Formulation

Ingredient	Lot #5	Lot#6	Lot #7
Ethylcellulose (ETHOCEL® PR 100)	15.60	15.60	15.60
Polyvinylpyrrolidone (KOLLIDON® 90F)	6.07	6.07	6.07
Dibutyl Sebacate	4.33	4.33	4.33
Ethyl Alcohol 200 Proof	249.75*	249.75*	249.75*
Isopropyl Alcohol 99%	13.15*	13.15*	13.15*

- 15 \* evaporated during process

### Coating Preparation

The tablet core coating solution was prepared according to the process described in Example 1.

Table 16: Coating Parameters

Parameter	Lot #5	Lot#6	Lot #7
Inlet Temperature C°	49-50	50-51.5	50-51.5
Outlet Temperature C°	38.5-39.5	39.5-40.5	39.5-40.5
Bed Temperature C°	37.5-38.5	37.5-39	37.5-39
Spray Rate g/min	300	300	300
Atomizing Air/Pattern Psi	25/25	25/25	25/25
Distance gun/Bed	6"	6"	6"
Distance between guns	6"	6"	6"
Pan speed rpm	12.0	12.0	12.0

5

### Dissolution Method

The dissolution method was performed according to the method described in Example 1.

Table 17: Dissolution Profile

Time (min.)	% Dissolved			10
	Lot #5	Lot#6	Lot #7	
0	0	0	0	
120	5.54	4.13	5.37	
240	14.71	14.29	15.76	
360	29.25	31.83	33.48	
480	46.40	50.16	51.62	
600	N/A	65.64	66.42	
720	N/A	76.8	77.49	

Figure 14 illustrates the *in vitro* dissolution profiles of 200 mg Tramadol HCl ER Tablets formulated according to Lot Nos. 5 to 7.

### EXAMPLE 7:

15 A two-way, crossover, open-label, single-dose, fasting, comparative bioavailability study of Tramadol HCl Extended-Release Tablets (2 x 100 mg vs 1 x 200 mg) in normal healthy non-smoking male subjects was conducted.

### 7.1: Synopsis

Based on preliminary data from 12 completing subjects, the 200 mg strength Tramadol HCl ER Tablets are proportional to the 100 mg strength given as 2 x 100 mg.

### 5 7.2: Purpose of Study

This study was designed to determine the dosage strength proportionality of two strengths of Tramadol HCl ER Tablets (2 x 100 mg vs 1 x 200 mg) under single dose fasting conditions.

### 7.3: Study Design

10 A single-dose, open-label, two-way, two-sequence, crossover design. The treatments were separated by a one (1) week washout period. On day 1 of each period, subjects received one of the following treatments on two (2) separate occasions according to the randomization scheme

15 Treatment A: Two Tramadol HCl Extended Release 100 mg Tablets with 240 mL of water at 0.0 hour following a 10 hour overnight fast  
(Total Daily Dose = 200 mg)

20 Treatment B: One Tramadol HCl Extended Release 200 mg Tablet with 240 mL of water at 0.0 hour following a 10 hour overnight fast  
(Total Daily Dose = 200 mg)

### 7.4: Summary and Conclusions

This study was intended to determine the dosage strength proportionality of two strengths of Tramadol HCl ER Tablets (2 x 100 mg vs 1 x 200 mg) under single dose fasting conditions. A total of 12 male subjects were dosed at Biovail  
25 Contract Research. Pharmacokinetic and statistical analyses were conducted with preliminary plasma data from 12 completing subjects for Tramadol, and M1 metabolite. The mean plasma concentrations vs time plots based on 12 completing subjects for tramadol, and M1 metabolite are presented in Figures 15 and 16, respectively. Individual pharmacokinetic parameters are shown in  
30 Tables 18a, 18b, 19a and 19b.

With all subjects, the ratio of geometric means (1 x 200 mg / 2 x 100 mg) for tramadol  $AUC_{0-t}$  and  $C_{max}$  were 1.11 and 1.17, respectively. The corresponding 90% confidence intervals were 97% - 125% and 103% - 133%, respectively. For the M1 metabolite, the ratio of geometric means (1 x 200 mg / 2 x 100 mg) for  $AUC_{0-t}$  and  $C_{max}$  were 1.05 and 1.11, respectively. The corresponding 90% confidence intervals were 96% - 116% and 102% - 121%, respectively.

In conclusion, the 200 mg strength Tramadol HCl ER Tablets were proportional to the 100 mg strength given as 2 x 100 mg since the 90 % confidence intervals for  $AUC_{0-t}$  and  $C_{max}$  for all analytes were found to be within 80 % - 125%.

Table 18a: Tramadol PK (n=12)

Cmax							
Tramadol ER							
		200mg		2x100 mg		200mg/2x100mg	
Subject	Tmax	Cmax	In Cmax	Tmax	Cmax	In Cmax	Cmax Ratio
1	8	244.69	5.50	8	258.32	5.55	0.95
2	10	277.87	5.63	12	339.09	5.83	0.82
3	8	243.47	5.50	10	330.78	5.80	0.74
4	10	268.04	5.59	10	226.90	5.42	1.18
5	6	227.80	5.43	8	200.75	5.30	1.13
6	8	259.13	5.56	10	216.91	5.38	1.19
7	5	261.09	5.56	10	155.44	5.05	1.68
8	8	226.11	5.42	8	98.86	4.59	2.29
9	8	278.90	5.63	10	232.96	5.45	1.20
10	10	195.36	5.27	8	148.30	5.00	1.32
11	8	353.25	5.87	8	330.44	5.80	1.07
12	10	435.46	6.08	10	404.39	6.00	1.08
Mean	8.25	272.60	5.59	9.33	245.26	5.43	1.22
SD	1.60	64.10	0.21	1.30	90.97	0.41	0.41
CV	19.42	23.51	3.77	13.96	37.09	7.50	33.90
Min	5.00	195.36	5.27	8.00	98.86	4.59	0.74
Max	10.00	435.46	6.08	12.00	404.39	6.00	2.29
Geo Mean	8.09	266.71	5.58	9.25	228.55	5.42	1.17
Cmax Ratio							
		Mean	Geo Mean		90% C.I.	90% C.I. (Excluding Subject 8)	
200mg/2x100mg		1.11	1.17(SAS)		103-133	100 - 123	

Table 18b: Tramadol PK (n=12)

Tramadol ER					
200mg		2x100mg		200mg/2x100mg	
Subject	AUCt	In AUCt	AUCt	In AUCt	AUCt Ratio
1	4604.23	8.43	4446.02	8.40	1.04
2	6485.28	8.78	6343.27	8.76	1.02
3	5324.71	8.58	6067.74	8.71	0.88
4	6975.11	8.85	6292.41	8.75	1.11
6	4284.83	8.36	4045.08	8.31	1.06
6	3919.08	8.27	3944.65	8.28	0.99
2	4096.54	8.32	3521.10	8.17	1.16
8	3279.62	8.10	1382.53	7.23	2.37
9	4260.44	8.36	4423.57	8.39	0.96
10	2923.70	7.98	2714.23	7.91	1.08
11	4911.47	8.50	4882.50	8.49	1.01
12	8824.82	9.09	8323.14	9.03	1.06
Mean	4990.82	8.47	4698.85	8.37	1.14
SD	1687.36	0.32	1852.43	0.47	2.37
CV	33.81	3.73	39.42	5.60	34.34
Min	2923.70	7.98	1382.53	7.23	0.88
Max	8824.82	9.09	8323.14	9.03	2.37
Geo Mean	4759.37	8.46	4307.55	8.36	1.10
AUCt Radio					
		Mean	Geo Mean	90% C.I.	90% C.I. (Excluding Subject 8)
200mg/2x100mg		1.06	1.11(SAS)	97-125	99 - 107

Figure 15 illustrates the comparison of the mean tramadol plasma concentration-time profiles resulting from the oral administration of Tramadol HCl 100 mg ER tablets (2 x 100 mg once a day) and Tramadol HCl 200 mg ER tablets (1 x 200 mg once a day) formulated according to an embodiment of the present invention.

Table 19a: M1 PK (n=12)

Cmax Tramadol ER							
Subject	200mg			2x100 mg			200mg/2x100mg
	Tmax	Cmax	In Cmax	Tmax	Cmax	In Cmax	Cmax Ratio
1	10	104.54	4.65	12	110.02	4.70	0.95
2	10	98.85	4.59	12	105.22	4.66	0.94
3	10	96.35	4.57	10	97.49	4.58	0.99
6	20	23.51	3.16	16	25.50	3.24	0.92
5	12	75.83	4.33	20	66.86	4.20	1.13
6	10	142.03	4.96	10	118.45	4.77	1.20
7	10	110.74	4.71	10	84.57	4.44	1.31
8	10	102.54	4.63	8	58.72	4.07	1.75
9	8	127.10	4.84	10	135.05	4.91	0.94
10	10	93.51	4.54	10	90.31	4.50	1.04
11	10	139.85	4.94	10	107.20	4.67	1.30
12	16	30.01	3.40	16	27.27	3.31	1.10
Mean	11.33	95.40	4.44	12.00	85.56	4.34	1.13
SD	3.34	37.38	0.57	3.52	34.68	0.55	0.24
CV	29.47	39.18	12.91	29.30	40.53	12.66	21.07
Min	8.00	23.51	3.16	8.00	25.50	3.24	0.92
Max	20.00	142.03	4.96	20.00	135.05	4.91	1.75
Geo Mean	10.98	85.03	4.40	11.59	76.53	4.30	1.11
Cmax Ratio							
		Mean	Geo Mean		90% C.I.	90% C.I. (Excluding Subject 8)	
200mg/2x100mg		1.12	1.11		102-121	100 - 115	

Table 19b: M1 PK (n=12)

AUCt Tramadol ER					
Subject	200mg		2x100mg		200mg/2x100mg
	AUCt	In AUCt	AUCt	In AUCt	AUCt Ratio
1	2386.29	7.78	2404.81	7.79	0.99
2	2367.19	7.77	2244.63	7.72	1.05
3	2150.65	7.67	2139.59	7.67	1.01
4	718.62	6.58	750.69	6.62	0.96
5	1862.16	7.53	1773.47	7.48	1.05
6	2474.58	7.81	2359.88	7.77	1.0
7	2079.14	7.64	2137.31	7.67	0.97
8	1717.15	7.45	958.31	6.87	1.79
9	2262.49	7.72	2661.79	7.89	0.85
10	1657.30	7.41	1800.10	7.50	0.92
11	2373.89	7.77	2072.75	7.64	1.15
12	722.24	6.58	666.77	6.50	1.08
Mean	1897.64	7.48	1830.84	7.42	1.07
SD	611.42	0.44	674.61	0.48	0.24
CV	32.22	5.87	36.85	6.45	22.33
Min	718.62	6.58	666.77	6.50	0.85
Max	2474.58	7.81	2661.79	7.89	1.79
Geo Mean	1766.50	7.46	1676.26	7.41	1.05
AUCt Ratio					
		Mean	Geo Mean	90% C.I.	90% C.I. (Excluding Subject 8)
200mg/2x100mg		1.04	1.05	96-116	96 - 105

5 Figure 16 illustrates the comparison of the mean M1 plasma concentration-time profiles resulting from the oral administration of Tramadol

HCl 100 mg ER tablets (2 x 100 mg once a day) and Tramadol HCl 200 mg ER tablets (1 x 200 mg once a day) formulated according to an embodiment of the present invention.

EXAMPLE 8:

- 5        A two-way, crossover, open-label, single-dose, fasting, comparative bioavailability study of Tramadol HCl Extended-Release Tablets (2 x 100 mg vs 1 x 200 mg) in normal healthy non-smoking male subjects was conducted.

8.1: Synopsis

- 10        Based on preliminary data from 23 completing subjects, the 200 mg strength Tramadol HCl ER Tablets are proportional to the 100 mg strength given as 2 x 100 mg.

8.2: Purpose of Study

- 15        This study was designed to determine the dosage strength proportionality of two strengths of Tramadol HCl ER Tablets (2 x 100 mg vs 1 x 200 mg) under single dose fasting conditions.

8.3: Study Design

- 20        A single-dose, open-label, two-way, two-sequence, crossover design. The treatments were separated by a one (1) week washout period. On day 1 of each period, subjects received one of the following treatments on two (2) separate occasions according to the randomization scheme

Treatment A:        Two Tramadol HCl Extended Release 100 mg Tablets with 240 mL of water at 0.0 hour following a 10 hour overnight fast  
(Total Daily Dose = 200 mg)

- 25        Treatment B:        One Tramadol HCl Extended Release 200 mg Tablet with 240 mL of water at 0.0 hour following a 10 hour overnight fast  
(Total Daily Dose = 200 mg)

8.4: Summary and Conclusions

- 30        This study was intended to determine the dosage strength proportionality of two strengths of Tramadol HCl ER Tablets (2 x 100 mg vs 1 x 200 mg) under single dose fasting conditions. A total of 24 male subjects were dosed at Biovail



Contract Research. Pharmacokinetic and statistical analyses were conducted with preliminary plasma data from 23 completing subjects for Tramadol, M1 and M5 metabolites. The mean plasma concentrations vs time plots based on 23 completing subjects for tramadol, M1 and M5 metabolites are presented in  
5 Figures 17, 18 and 19, respectively. Individual pharmacokinetic parameters are shown in Tables 20, 21 and 22.

With all subjects, the ratio of geometric means (1 x 200 mg / 2 x 100 mg) for tramadol  $AUC_{0-t}$  and  $C_{max}$  were 1.00 and 1.00, respectively. The corresponding 90% confidence intervals were 96.3 % - 104.17 % and 92.2 % -  
10 109.12 %, respectively. For the M1 metabolite, the ratio of geometric means (1 x 200 mg / 2 x 100 mg) for  $AUC_{0-t}$  and  $C_{max}$  were 1.00 and 0.97, respectively. The corresponding 90% confidence intervals were 95.6 % - 104.61 % and 90.3 % - 104.39 %, respectively. For the M5 metabolite, the ratio of geometric means (1 x 200 mg / 2 x 100 mg) for  $AUC_{0-t}$  and  $C_{max}$  were 0.98 and 0.99, respectively. The  
15 corresponding 90% confidence intervals were 92.6 % - 104.72 % and 90.9 % - 107.25 %, respectively.

In conclusion, the 200 mg strength Tramadol HCl ER Tablets were proportional to the 100 mg strength given as 2 x 100 mg since the 90 % confidence intervals for  $AUC_{0-t}$  and  $C_{max}$  for all analytes were found to be within  
20 80 % - 125 %.

Table 20: Summary of Pharmacokinetic Parameters for Tramadol

Tramadol								
Subject	B			A			B / A Ratio	
	Tramadol HCl ER 1 x 200 mg			Tramadol HCl ER 2 x 100 mg				
	AUC	Cmax	Tmax	AUC	Cmax	Tmax	AU C	Cmax
1	3772.72	125.97	24.00	4465.15	207.76	8.00	0.84	0.61
2	6989.42	361.35	14.00	7563.59	416.83	12.00	0.92	0.87
3	9967.41	440.03	14.00	8773.22	374.54	16.00	1.14	1.17
4	10503.26	528.11	16.00	10727.13	517.12	14.00	0.98	1.02
5	4315.08	244.26	12.00	4439.38	209.95	16.00	0.97	1.16
7	3539.99	151.93	16.00	4128.98	234.12	8.00	0.86	0.65
8	7752.67	368.21	14.00	6369.64	369.49	8.00	1.22	1.00
9	5413.87	281.50	14.00	5561.14	244.18	16.00	0.97	1.15
10	3640.04	162.12	12.00	4354.42	179.31	14.00	0.84	0.90
11	3442.46	147.72	20.00	3394.52	162.28	16.00	1.01	0.91
12	2763.51	190.15	10.00	2722.78	150.02	10.00	1.01	1.27
13	3746.10	203.07	8.00	4084.60	183.27	16.00	0.92	1.11
14	6394.67	311.42	16.00	5107.43	239.83	8.00	1.25	1.30
15	3093.78	178.86	12.00	2806.92	128.49	16.00	1.10	1.39
16	8363.96	465.15	10.00	7811.02	369.66	14.00	1.07	1.26
17	2410.07	130.62	14.00	2647.52	135.74	14.00	0.91	0.96
18	9336.37	469.34	8.00	9475.49	409.69	16.00	0.99	1.15
19	9125.11	437.92	14.00	8440.88	322.16	14.00	1.08	1.36
20	4983.63	209.73	10.00	4444.82	226.82	12.00	1.12	0.92
21	3337.64	151.75	12.00	3818.74	220.36	12.00	0.87	0.69
22	2868.24	164.88	16.00	2595.66	163.49	8.00	1.11	1.01
23	4233.82	179.29	16.00	4310.37	238.80	16.00	0.98	0.75
24	7311.78	329.98	20.00	7105.46	307.21	20.00	1.03	1.07
Mean	5535.03	271.02	14.00	5441.25	261.35	13.22	1.01	1.03
SD	2591.09	128.34	3.86	2376.20	104.90	3.45	0.11	0.22
CV	46.81	47.36	27.58	43.67	40.14	26.10	11.3 2	21.60
Geo Mean	4992.59	244.00	13.51	4979.67	242.83	12.74	1.00	1.00
Min	2410.07	125.97	8.00	2595.66	128.49	8.00	0.84	0.61
Max	10503.26	528.11	24.00	10727.13	517.12	20.00	1.25	1.39
	1 x 200 mg / 2 x 100 mg Ratio							
	Means	Geo Means	LS Means %	90% CI				
	AUC	1.02	1.00	100.11	96.3-104.17			
	Cmax	1.04	1.00	100.29	92.2-109.12			

Figure 17 illustrates the mean plasma Tramadol concentrations (ng/ml) over time after two 100 mg Tramadol HCl ER Tablets formulated according to an

embodiment of the present invention or after one 200 mg Tramadol HCl ER Tablet formulated according to an embodiment of the present invention following a 10 hour overnight fast.

Table 21: Summary of Pharmacokinetic Parameters for M1

M1									
Subject	B			A					
	Tramadol HCl ER 1 x 200 mg			Tramadol HCl ER 2 x 100 mg			B/ A Ratio		
	AUC	Cmax	Tmax	AUC	Cmax	Tmax	AU C	Cmax	
1	1672.89	57.88	24.00	2022.04	80.50	16.00	0.83	0.72	
2	970.95	43.44	14.00	1156.80	54.21	12.00	0.84	0.80	
3	1774.74	69.27	20.00	1789.62	70.05	20.00	0.99	0.99	
4	1076.19	48.16	16.00	1050.38	44.32	16.00	1.02	1.09	
5	1979.48	96.47	14.00	1657.77	72.52	14.00	1.19	1.33	
7	953.92	36.57	24.00	1330.47	68.82	8.00	0.72	0.53	
8	1414.94	61.68	24.00	1116.16	53.67	12.00	1.27	1.15	
9	2484.11	113.99	14.00	2406.74	108.07	20.00	1.03	1.05	
10	1721.50	73.76	14.00	1906.22	74.23	16.00	0.90	0.99	
11	1829.82	80.76	24.00	1850.88	88.60	16.00	0.99	0.91	
12	2144.82	109.30	10.00	2095.44	101.89	14.00	1.02	1.07	
13	2111.31	90.98	10.00	2036.17	89.08	20.00	1.04	1.02	
14	2130.45	93.13	16.00	2122.92	91.06	16.00	1.00	1.02	
15	2360.46	115.08	12.00	2128.12	97.80	16.00	1.11	1.18	
16	3234.30	130.32	12.00	3507.19	134.18	20.00	0.92	0.97	
17	1922.21	90.47	16.00	1977.41	91.02	14.00	0.97	0.99	
18	3490.68	135.80	12.00	3521.34	138.38	16.00	0.99	0.98	
19	1154.33	49.30	16.00	991.16	38.21	20.00	1.16	1.29	
20	2303.91	96.21	14.00	2269.27	110.63	14.00	1.02	0.87	
21	1853.29	72.48	16.00	1983.58	95.39	12.00	0.93	0.76	
22	2637.81	153.39	16.00	2464.84	144.41	8.00	1.07	1.06	
23	1970.96	81.98	24.00	1870.67	96.76	16.00	1.05	0.85	
24	1867.23	89.74	20.00	1673.09	78.73	20.00	1.12	1.14	
Mean	1959.14	86.53	16.61	1953.40	87.94	15.48	1.01	0.99	
SD	639.46	30.56	4.69	647.00	27.94	3.58	0.12	0.18	
CV	32.64	35.32	28.23	33.12	31.77	23.12	12.1 1	18.40	
Geo Mean	1857.57	81.15	16.00	1855.19	83.46	15.03	1.00	0.97	
Min	953.92	36.57	10.00	991.16	38.21	8.00	0.72	0.53	
Max	3490.68	153.39	24.00	3521.34	144.41	20.00	1.27	1.33	
	1 x 200 mg/ 2 x 100 mg Ratio								
	Means	Geo Means	LS Means %	90% CI					

AUC	1.00	1.00	100.01	95.6-104.61		
Cmax	0.98	0.97	97.06	90.3-104.39		

Figure 18 illustrates the mean plasma M1 concentrations (ng/ml) over time after two 100 mg Tramadol HCl ER Tablets formulated according to an embodiment of the present invention or after one 200 mg Tramadol HCl ER Tablet formulated according to an embodiment of the present invention following a 10 hour overnight fast.

Table 22: Summary of Pharmacokinetic Parameters for M5:

M5									
	B				A			B/ A Ratio	
	Tramadol HCl ER 1 x 200 mg				Tramadol HCl ER 2 x 100 mg				
Subject	AUC	Cmax	Tmax		AUC	Cmax	Tmax	AU C	Cmax
1	586.48	19.01	30.00		669.49	26.43	16.00	0.88	0.72
2	1011.03	39.82	20.00		1156.49	43.27	16.00	0.87	0.92
3	479.82	18.04	20.00		606.97	21.98	24.00	0.79	0.82
4	597.78	23.35	24.00		709.78	25.47	24.00	0.84	0.92
5	638.62	28.06	12.00		652.44	28.32	16.00	0.98	0.99
7	505.59	18.07	20.00		794.87	34.53	14.00	0.64	0.52
8	1105.91	49.06	24.00		1022.61	39.84	14.00	1.08	1.23
9	765.91	32.10	14.00		860.60	35.68	20.00	0.89	0.90
10	986.85	41.59	14.00		973.22	38.01	16.00	1.01	1.09
11	492.42	20.37	24.00		565.44	24.25	16.00	0.87	0.84
12	1566.17	75.38	16.00		1481.53	71.45	14.00	1.06	1.06
13	1044.20	43.60	16.00		974.90	39.62	20.00	1.07	1.10
14	843.42	35.36	16.00		809.01	33.16	16.00	1.04	1.07
15	967.94	46.14	14.00		867.23	36.72	16.00	1.12	1.26
16	987.92	44.60	20.00		1019.98	38.32	20.00	0.97	1.16
17	630.21	29.71	16.00		607.88	25.47	20.00	1.04	1.17
18	1889.26	66.43	14.00		1865.13	67.08	20.00	1.01	0.99
19	813.41	31.21	20.00		584.26	19.99	20.00	1.39	1.56
20	841.90	34.50	14.00		640.29	27.74	14.00	1.31	1.24
21	829.00	33.19	16.00		940.72	42.90	14.00	0.88	0.77
22	617.32	33.20	16.00		639.87	37.09	10.00	0.96	0.90
23	908.93	38.57	24.00		759.38	40.38	16.00	1.20	0.96
24	743.29	33.02	20.00		717.33	30.83	20.00	1.04	1.07
Mean	863.19	36.28	18.43		866.06	36.02	17.22	1.00	1.01
SD	334.21	14.20	4.51		308.56	12.52	3.45	0.17	0.22
CV	38.72	39.15	24.47		35.63	34.76	20.04	16.5 9	21.38
Geo Mean	812.38	33.87	17.94		825.19	34.29	16.88	0.98	0.99
Min	479.82	18.04	12.00		565.44	19.99	10.00	0.64	0.52

Max	1889.26	75.38	30.00		1865.13	71.45	24.00		1.39	1.56
	1 x 200 mg / 2 x 100 mg Ratio									
	Means	Geo Means	LS Means %	90% CI						
AUC	1.00	0.98	98.45	92.6-104.72						
Cmax	1.01	0.99	98.77	90.9-107.25						

Figure 19 illustrates the mean plasma M5 concentrations (ng/ml) over time after two 100 mg Tramadol HCl ER Tablets formulated according to an embodiment of the present invention or after one 200 mg Tramadol HCl ER Tablet formulated according to an embodiment of the present invention following a 10 hour overnight fast.

#### EXAMPLE 9:

A two-way, crossover, open-label, single-dose, food effect, comparative bioavailability study of Tramadol HCl Extended-Release 200 mg Tablets in normal healthy non-smoking male subjects was conducted.

#### 9.1: Synopsis

Based on preliminary data from 20 completing subjects, the presence of food significantly decreased the rate and extent of absorption of tramadol, M1 and M5 metabolites of Tramadol HCl ER tablets 200 mg following single dose administration.

#### 9.2: Purpose of Study

This study was designed to evaluate the effect of food on Tramadol HCl ER 200 mg Tablets following single dose administration.

#### 9.3: Study Design

A single-dose, open-label, two-way, two-sequence, crossover design. The treatments were separated by a one (1) week washout period. On day 1 of each period, subjects received one of the following treatments following a 10 hour overnight fast on two (2) separate occasions according to the randomization scheme

Treatment A: One Tramadol HCl Extended Release 200 mg Tablet with 240 mL of water at 0.0 hour within 5 minutes of complete ingestion of a high fat content breakfast.

5 Treatment B: One Tramadol HCl Extended Release 200 mg Tablet with 240 mL of water at 0.0 hour following a 10 hour overnight fast.

#### 9.4: Summary and Conclusions

This study was intended to evaluate the effect of food on Tramadol HCl ER 200 mg Tablets following single dose administration. A total of 24 male subjects were dosed at Biovail Contract Research. Pharmacokinetic and statistical analyses were conducted with preliminary plasma data from 22 completing subjects. The mean plasma concentrations vs time plots based on 20 completing subjects for tramadol, M1 and M5 metabolites are presented in Figures 20, 21 and 22, respectively. Individual pharmacokinetic parameters are shown in Tables 23, 24 and 25.

15 With all subjects, the ratio of geometric means (Fed / Fasting) for tramadol  $AUC_{0-t}$  and  $C_{max}$  were 0.76 and 0.73, respectively. For the M1 metabolite, the ratio of geometric means (Fed / Fasting) for  $AUC_{0-t}$  and  $C_{max}$  were 0.75 and 0.76, respectively. For the M5 metabolite, the ratio of geometric means (Fed / Fasting) for  $AUC_{0-t}$  and  $C_{max}$  were 0.73 and 0.73, respectively.

20 When data analysis was carried out in the absence of subject #12 and #18, the ratio of geometric means for tramadol  $AUC_{0-t}$  and  $C_{max}$  were 0.79 and 0.73, respectively. For the M1 metabolite, the ratio of geometric means (Fed / Fasting) for  $AUC_{0-t}$  and  $C_{max}$  were 0.78 and 0.76, respectively. For the M5 metabolite, the ratio of geometric means (Fed / Fasting) for  $AUC_{0-t}$  and  $C_{max}$  were 0.75 and 0.72, respectively.

25 Based on the results, it was concluded that a significant food effect was observed for Tramadol HCl ER 200 mg Tablets. In the presence of food, the rate and extent of absorption of tramadol and its metabolites resulting from a single dose of Tramadol HCl ER 200 mg Tablet were significantly lower when compared to administration without food.

30

Table 23: Summary of Pharmacokinetic Parameters for Tramadol

Tramadol								
	Tramadol ER 200 mg, Fed				Tramadol ER 200 mg, Fasting			Fed / Fasting
Subject	AUC	C <sub>max</sub>	T <sub>max</sub>		AUC	C <sub>max</sub>	T <sub>max</sub>	AU C
1	3944.30	149.33	24.00		4013.96	205.64	14.00	0.98
2	4078.64	139.34	24.00		6969.14	355.35	14.00	0.59
3	6818.20	251.76	20.00		6939.38	342.62	10.00	0.98
4	2021.34	72.15	24.00		4218.92	234.01	14.00	0.48
5	2330.34	142.73	20.00		2848.84	140.20	16.00	0.82
6	4636.19	225.35	20.00		5154.28	340.84	12.00	0.90
7	1901.40	128.41	14.00		3554.14	173.63	16.00	0.53
8	4585.55	137.09	14.00		5674.75	263.32	14.00	0.81
9	7727.96	320.14	14.00		7827.31	290.33	20.00	0.99
10	3783.07	170.80	14.00		4258.28	203.68	16.00	0.89
11	7079.58	263.39	14.00		7252.23	285.04	14.00	0.98
13	3342.06	171.38	16.00		3019.69	138.26	12.00	1.11
15	4424.02	190.87	16.00		4935.58	255.62	14.00	0.90
16	7296.94	328.00	16.00		6632.83	342.80	12.00	1.10
17	1070.08	43.56	4.00		8377.65	384.17	10.00	0.13
20	4209.33	215.06	14.00		5340.01	288.25	12.00	0.79
21	3451.99	173.23	14.00		3886.46	205.50	16.00	0.89
22	3937.39	155.94	16.00		3596.43	152.88	14.00	1.09
23	4539.31	200.08	20.00		5569.65	244.83	16.00	0.82
24	8472.81	669.76	24.00		6400.85	312.84	16.00	1.32
Mean	4482.52	207.42	17.10		5323.52	257.99	13.80	0.85
SD	2042.83	130.14	4.96		1647.23	75.37	2.50	0.26
CV	45.57	62.74	29.02		30.94	29.21	18.15	30.9 3
Geo Mean	3999.75	178.85	16.16		5076.49	246.69	13.59	0.79
Min	1070.08	43.56	4.00		2848.84	138.26	10.00	0.13
Max	8472.81	669.76	24.00		8377.65	384.17	20.00	1.32
	Fed / Fasting Ratio			Fed / Fasting Ratio (Including Subject #12 and #18 who vomited during post-dose)				
		Geo Means	LS Means %		Geo Means	LS Means %		
	AUC	0.79	78.93		AUC	0.76	75.62	
	C <sub>max</sub>	0.73	72.27		C <sub>max</sub>	0.73	72.38	

Figure 20 illustrates the mean plasma Tramadol concentrations (ng/ml) over time after a single dose of one 200 mg Tramadol HCl ER Tablet formulated

according to an embodiment of the present invention under fasting or fed conditions.

Table 24: Summary of Pharmacokinetic Parameters for M1:

M1								
	Tramadol ER 200 mg, Fed			Tramadol ER 200 mg, Fasting			Fed / Fasting	
Subject	AUC	Cmax	Tmax	AUC	Cmax	Tmax	AUC	Cmax
1	1921.05	75.67	24.00	2116.84	90.06	20.00	0.91	0.84
2	1278.59	45.95	24.00	2158.62	86.81	20.00	0.59	0.53
3	1159.73	42.64	20.00	1183.17	46.50	10.00	0.98	0.92
4	542.48	19.92	24.00	1223.87	58.17	14.00	0.44	0.34
5	1894.84	117.77	20.00	1982.93	96.08	20.00	0.96	1.23
6	1887.04	91.91	20.00	1761.13	105.91	12.00	1.07	0.87
7	1130.02	60.88	16.00	1901.17	77.45	16.00	0.59	0.79
8	1674.77	51.91	24.00	2013.76	75.57	16.00	0.83	0.69
9	1511.07	52.51	24.00	1487.99	53.84	24.00	1.02	0.98
10	1322.65	54.89	16.00	1702.91	70.92	16.00	0.78	0.77
11	1335.58	51.01	20.00	1286.31	46.10	24.00	1.04	1.11
13	2269.80	100.16	16.00	1796.92	70.38	14.00	1.26	1.42
15	1018.82	46.97	20.00	1168.38	52.96	16.00	0.87	0.89
16	1270.79	56.22	16.00	1382.61	71.49	16.00	0.92	0.79
17	183.63	5.70	24.00	1555.20	63.67	14.00	0.12	0.09
20	2275.30	101.30	20.00	2439.33	116.53	14.00	0.93	0.87
21	1257.39	60.38	20.00	1339.50	64.90	12.00	0.94	0.93
22	1749.84	66.63	20.00	2118.35	79.93	24.00	0.83	0.83
23	2201.99	91.33	24.00	2577.88	107.78	20.00	0.85	0.85
24	1373.21	77.04	24.00	1575.86	65.39	20.00	0.87	1.18
Mean	1462.93	63.54	20.80	1738.64	75.02	17.10	0.84	0.84
SD	543.09	27.58	3.07	419.16	20.30	4.18	0.25	0.29
CV	37.12	43.40	14.76	24.11	27.07	24.44	29.56	34.89
Geo Mean	1311.89	55.00	20.57	1691.12	72.48	16.61	0.78	0.76
Min	183.63	5.70	16.00	1168.38	46.10	10.00	0.12	0.09
Max	2275.30	117.77	24.00	2577.88	116.53	24.00	1.26	1.42
Fed / Fasting Ratio								
Fed / Fasting Ratio				Fed / Fasting Ratio (Including Subject #12 and #18 who vomited during post-dose)				
		Geo Means	LS Means %		Geo Means	LS Means %		
AUC		0.78	77.89	AUC	0.75	75.27		
Cmax		0.76	76.07	Cmax	0.76	76.25		

5 Figure 21 illustrates the mean plasma M1 concentrations (ng/ml) over time after a single dose of one 200 mg Tramadol HCl ER Tablet formulated



according to an embodiment of the present invention under fasting or fed conditions.

Table 25: Summary of Pharmacokinetic Parameters for M5:

M5								
	Tramadol ER 200 mg, Fed				Tramadol ER 200 mg, Fasting			
Subject	AUC	Cmax	Tmax		AUC	Cmax	Tmax	Fed / Fasting
								AU C Cmax
1	748.53	27.50	20.00		897.15	39.14	20.00	0.83 0.70
2	511.56	16.27	24.00		915.79	36.24	20.00	0.56 0.45
3	658.62	21.94	24.00		678.13	22.05	24.00	0.97 1.00
4	536.16	20.64	36.00		1281.12	58.25	20.00	0.42 0.35
5	371.79	21.38	20.00		406.02	17.27	20.00	0.92 1.24
6	851.56	38.97	20.00		732.06	40.97	12.00	1.16 0.95
7	298.02	16.33	16.00		535.16	21.77	16.00	0.56 0.75
8	764.80	21.96	24.00		1100.54	38.46	24.00	0.69 0.57
9	1066.70	31.87	24.00		1054.70	33.20	24.00	1.01 0.96
10	547.25	21.77	20.00		674.38	26.28	16.00	0.81 0.83
11	582.46	22.11	24.00		565.57	19.86	24.00	1.03 1.11
13	446.45	19.72	16.00		399.37	16.12	14.00	1.12 1.22
15	629.68	26.27	20.00		746.10	30.50	16.00	0.84 0.86
16	943.41	33.73	20.00		1024.16	44.47	16.00	0.92 0.76
17	41.47	1.49	24.00		341.34	12.37	14.00	0.12 0.12
20	939.16	36.75	20.00		1125.74	52.09	14.00	0.83 0.71
21	599.05	26.91	20.00		617.38	26.32	14.00	0.97 1.02
22	674.58	23.94	20.00		782.20	28.83	16.00	0.86 0.83
23	555.68	21.00	24.00		755.53	30.14	20.00	0.74 0.70
24	644.69	24.87	24.00		826.43	31.25	20.00	0.78 0.80
Mean	620.58	23.77	22.00		772.94	31.28	18.20	0.81 0.80
SD	236.47	8.13	4.21		259.24	11.96	3.89	0.25 0.28
CV	38.10	34.21	19.11		33.54	38.23	21.36	30.6 35.05
Geo Mean	542.98	21.07	21.67		728.60	29.09	17.81	0.75 0.72
Min	41.47	1.49	16.00		341.34	12.37	12.00	0.12 0.12
Max	1066.70	38.97	36.00		1281.12	58.25	24.00	1.16 1.24
Fed / Fasting Ratios				Fed / Fasting Ratios (Including Subject #12 and #18 who vomited during post-dose)				
		Geo Means	LS Means %			Geo Means	LS Means %	
AUC		0.75	74.62		AUC	0.73	73.24	
Cmax		0.72	72.23		Cmax	0.73	73.45	

5 Figure 22 illustrates the mean plasma M5 concentrations (ng/ml) over time after a single dose of one 200 mg Tramadol HCl ER Tablet formulated

according to an embodiment of the present invention under fasting or fed conditions.

EXAMPLE 10: Tramadol ER Osteoarthritis Study

10.1: Overall Study Design and plan

5       A 12-week, multi-center double blind, randomized, dose-titration, parallel-group comparison of the efficacy and safety of Tramadol ER tablets and placebo in the treatment of osteoarthritis of the knee was conducted. Approximately 245 patients from 18 to 75 years of age with moderate to severe pain associated with Functional Class I-III osteoarthritis of the knee were  
10       planned for study enrollment to ensure that a minimum of 140 patients completed the study. After signing the informed consent, patients who met the inclusion and exclusion criteria at screening entered a 2 to 7 day washout period during which all analgesic use was discontinued. At the start of the first week of the study (Baseline, Visit 2), eligible patients who reported pain intensity  $\geq 40$   
15       mm on a visual analog scale (VAS) in the index knee joint were randomly assigned to either Tramadol ER tablets or placebo.

      Patients assigned to Tramadol ER tablets were initiated on 100 mg QD and maintained on their dose for at least 3 days. On Day 4, and for the remainder of the week (until their return to the clinic for Visit 3), patients were permitted to  
20       have their dose increased to 200 mg QD, based upon the tolerability of side effects. Beginning at Visit 3, patients must have been maintained on a minimum Tramadol ER tablet dose of 200 mg QD, and the dose titrated upwards if required based upon the adequacy of pain relief and tolerability of side effects. Patients randomized to the placebo group underwent sham dose increases.  
25       Further dose escalation and de-escalation was permitted provided that a minimum dose of 200 mg QD was maintained from Week 1 (Visit 3) to Week 12 (Visit 7). In patients with pain unresponsive to appropriate dosage adjustments, or with unacceptable side effects, treatment was discontinued and alternate analgesia therapy initiated, as appropriate. Patients returned for efficacy and  
30       safety evaluations at Week 1 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5), Week 8 (Visit 6) and Week 12 (Visit 7) or at Early Termination.

## 10.2: Efficacy Variables

The primary measure of efficacy was the Arthritis Pain Intensity VAS (visual analog scale) Score from patient visits. The arthritis VAS is the most commonly used, validated tool to assess pain intensity and one recommended by  
5 FDA to evaluate the analgesic potential of a drug product.

Pain was also assessed as a secondary measure of efficacy using the WOMAC Osteoarthritis Index. The WOMAC is a validated, internationally recognized and widely used multidimensional instrument for assessing response to therapy in osteoarthritis. It assesses pain, joint stiffness and physical function,  
10 the three major bothersome symptoms in osteoarthritis. In addition, patients and physicians provided a Global assessment of disease and patients recorded their response on a sleep questionnaire as other secondary measures of efficacy.

## 10.3: Results

A total of 246 patients were randomized and evaluable for safety. Of  
15 these, 219 were evaluable for the intent-to-treat (ITT) population. The ITT population included all safety evaluable patients who had primary efficacy information recorded at the baseline visit (Visit 2) and at the Week 1 visit (Visit 3), the first primary efficacy variable collection point on treatment. The ITT population also included all patients who dropped out before the Week 1 visit  
20 due to lack of treatment efficacy. The mean daily dose of Tramadol ER following the flexible dosing regimen was approximately 300 mg. The median age of patients who enrolled was 61 years and the median duration of osteoarthritis was 10 years.

Tramadol ER produced statistically significant and clinically meaningful  
25 reductions in pain intensity associated with osteoarthritis of the knee compared to placebo for the primary efficacy variable and all secondary variables evaluated.

## 10.4: Response to Primary Variable

Figure 23 compares the LS mean change from baseline in VAS score for  
30 Tramadol ER and placebo based upon the average of Weeks 1-12. On the primary endpoint (LS Mean change from baseline over 12 weeks), there was a

39.5% (30.4 mm) and 21.5% (17.7 mm) change from baseline in the arthritis pain intensity VAS in the Tramadol ER and placebo groups, respectively (LS Mean Difference 12.7 mm,  $p < 0.001$ ). Figure 24 shows the weekly LS mean changes from baseline for the two treatment groups. Treatment differences emerged at the first return visit (Week 1) when patients were receiving either a 100 mg or 200 mg dose of Tramadol ER (change from baseline 24.8% [19.6 mm] vs. 14.0% [11.1 mm], LS mean difference 8.5 mm,  $p = 0.003$ ). At the end of the second week of treatment, the response to Tramadol ER increased relative to placebo (change from baseline 35.7% [27.4 mm] vs. 19.3% [15.7 mm], LS mean difference 11.7 mm,  $p < 0.001$ ). By Week 12, the response to Tramadol ER (LS mean change from baseline) was 48.6% [37.4 mm] while that for placebo was 27.0% [22.1 mm]. The LS Mean difference was 15.3 mm,  $p < 0.001$ ).

#### 10.5: Response on the Secondary Variables

Figure 25 compares the LS mean changes from baseline to Week 12 for the Tramadol ER and placebo for each of the secondary variables.

##### 10.5.1: WOMAC Subscales

Results on the three dimensions of the WOMAC, namely pain, stiffness and physical function were similar to the main findings. Tramadol ER tablets was significantly better than placebo in improving pain, stiffness and physical function on the WOMAC.

At Week 12, on the WOMAC Pain Subscale, Tramadol ER was significantly different from placebo (change from baseline 44.6% [155.9 mm] vs. 24.8% [86.9 mm], LS mean difference on 0-100 mm Scale 13.8 mm,  $p < 0.001$ ).

At Week 12, on the WOMAC Stiffness Subscale, Tramadol ER was significantly different from placebo (change from baseline 43.4% [63.9 mm] vs. 18.1% [33.8 mm], LS mean difference on 0-100 mm Scale 15.0 mm,  $p < 0.001$ ).

At Week 12, on the WOMAC Physical Function Subscale, Tramadol ER was significantly different from placebo (change from baseline 43.8% [518.3 mm] vs. 21.3% [270.4 mm], LS mean difference on 0-100 mm Scale 14.6 mm,  $p < 0.001$ ).

At Week 12, on the WOMAC Composite Score, Tramadol ER was significantly different from placebo (change from baseline 42.2% [737.9 mm] vs. 22.8% [391.2 mm], LS mean difference on 0-100 mm Scale 14.4 mm,  $p < 0.001$ ).

### 3.5.2: WOMAC Pain Walking on a Flat Surface

5 In the past, some studies have utilized one item from the WOMAC pain subscale as the primary endpoint. Since some of the questions on the WOMAC subscale relate to walking "up" or "down stairs" (and some areas of the country preferred by the elderly have few stairs, e.g., Arizona, New Mexico, Florida, etc), the WOMAC pain subscale question, "Pain Walking on a Flat Surface" is  
10 preferred by some biometricians.

At Week 12, on the WOMAC Pain Walking on Flat Surface, Tramadol ER was significantly different from placebo (change from baseline 40.9% [29.9 mm] vs. 15.7% [15.9 mm], LS Mean Difference 14 mm,  $p < 0.001$ ). This is also shown in Figure 25.

### 15 10.5.3: Patient Global Assessment of Osteoarthritis

At Week 12, on the Patient Global Assessment of Arthritis, Tramadol ER was significantly different from placebo (change from baseline 33.0% [33.2 mm] vs. 24.4% [18.5 mm], LS Mean Difference 14.7 mm,  $p < 0.001$ ).

### 10.6: Safety Results

20 This was a placebo-controlled study without a positive control. Consequently, direct comparison with data on ULTRAM® product are not possible. However, indirect comparisons with the ULTRAM® product package insert are possible. Table 1 provides data on the cumulative incidence of adverse events on ULTRAM® in chronic non-malignant pain. The 90-day comparison is  
25 the most appropriate, given the 12 weeks duration of the present study. Adverse events were qualitatively similar. However, the incidence of the most commonly observed adverse events were generally lower for Tramadol ER after up to 90 days compared to only 7 days of treatment with ULTRAM®.

**Table 26. Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain (N = 427). Data on Tramadol HCl ER from the 12-Week OA Study (N=124) are Provided in Parenthesis for Comparison**

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33% (33%)
Nausea	24%	34%	40% (24.2%)
Constipation	24%	38%	46% (25.8%)
Headache	18%	26%	32% (14.5%)
Somnolence	16%	23%	25% (8.1%)
Vomiting	9%	13%	17% (6.5%)
Pruritus	8%	10%	11% (6.5%)
"CNS Stimulation" <sup>1</sup>	7%	11%	14% (TBD)
Asthenia	6%	11%	12% (TBD)
Sweating	6%	7%	9% (4%)
Dyspepsia	5%	9%	13% (1.6%)
Dry Mouth	5%	9%	10% (1.6%)
Diarrhea	5%	6%	10% (9.7%)

<sup>1</sup> "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

#### 10.7: Conclusion:

Tramadol ER produced statistically significant and clinically meaningful reductions in pain associated with osteoarthritis compared to placebo following a flexible dosing regimen in which the once-daily tablet formulation was titrated upward or downward over 12 weeks in doses of 200mg, 300mg or 400mg based upon adequacy of pain relief and tolerability of side effects. The mean daily dose of Tramadol ER was estimated to be about 300mg. The primary efficacy variable was pain relief as measured on a visual analog scale (VAS). Secondary measures of efficacy were the pain intensity, stiffness and physical function subscales of WOMAC Osteoarthritis Index, the Patient's and Physician's Global Assessment of Arthritis, patient withdrawal due to inadequate pain relief, and patient assessment of sleep.

At the end of the first week of treatment and at all subsequent weeks, Tramadol ER was statistically superior to placebo in reducing pain. The magnitude pain improvement (change from baseline) for the Tramadol ER cohort

increased weekly throughout the 12 weeks of therapy (25% at Week 1 and 47% at Week 12). By Week 12, patient's treated with Tramadol reported a clinically important 15 mm difference in mean pain relief score compared to placebo. This difference was highly significant ( $p < 0.001$ ). Based upon the average of Weeks 1 through 12, the Tramadol ER treated patients achieved a highly statistically significant and clinically meaningful 14 mm difference in mean pain relief score compared to placebo ( $p < 0.001$ ). The results for the secondary variables paralleled those of the primary with all results statistically significant in favor of Tramadol ER.

10 The adverse events reported were qualitatively similar to that for Ultram. However, the incidence was generally lower for Tramadol ER than for that previously reported for ULTRAM®.

The results of this 12 week placebo controlled study demonstrate that Tramadol ER, when given at a dose of 200 to 400 mg QD, results in significant improvements in the cardinal symptoms of osteoarthritis, namely pain, stiffness and physical function. The safety profile of Tramadol ER is consistent with that for ULTRAM®, although the frequency of some adverse events appears to be lower than historical controls.

#### 10.8: Clinical Implications

20 In the present study, using conventional endpoints for evaluating efficacy, Tramadol ER demonstrated a 30.4 mm and 37.4 mm change from baseline in Arthritis Pain Intensity VAS, when expressed as a mean over 12 weeks (primary endpoint) and at the 12-Week time point, respectively. However, consistent with most such studies, the placebo treatment demonstrates a 17.7 mm and 22.1 mm change from baseline in Arthritis Pain Intensity VAS, when expressed as a mean over 12 weeks (primary endpoint) and at the 12-Week time point, respectively. Consequently, the actual treatment difference (response on Tramadol ER less response on placebo) is a 12.7 mm and 15.3 mm change from baseline in Arthritis Pain Intensity VAS, when expressed as a mean over 12 weeks (primary endpoint) and at the 12-Week time point, respectively.

A close examination of the time course and magnitude of the pharmacological response (on the primary and secondary variables) following treatment with Tramadol ER indicates that this is a clear drug effect: the magnitude of the response increases over time and all of the effects (pain, stiffness, physical function, patient global) are directionally consistent and generally of comparable size.

There are two available benchmarks for determining the robustness of the analgesic response to Tramadol ER in osteoarthritis. One approach involves using the perspectives from the academic rheumatology community. The other involves using the results of pivotal studies in osteoarthritis from recently approved and commercially successful drugs.

In a consensus development (3-round Delphi exercise) involving academic rheumatologists, a 15 mm treatment difference in patients overall assessment of pain was considered to be the minimum clinically important difference (MCID) for clinical trial purposes (Bellamy N, Carette S, Ford PM et al. Osteoarthritis Antirheumatic Drug Trials. II. Tables for calculating sample size for clinical trials. J Rheumatol 1992;19:444-50; Bellamy N, Carette S, Ford PM et al. Osteoarthritis Antirheumatic Drug Trials. III. Delta for Clinical Trials - Results of a Consensus Development (Delphi) Exercise. J Rheumatology 1992; 19:3, 451-457). However, in a recently published study, the minimum clinically perceptible improvement (MCPI) on the three dimensions of WOMAC pain, stiffness and physical function subscale scores (expressed using a 0-100 mm scale) were 9.7, 9.3 and 10 mm, respectively (Beaton DE, Bombardier C, Katz J et al. Looking for important change/difference in studies of responsiveness. J Rheumatol 2001;28:400-405.).

Data from other approved analgesics for which the NDA contained pivotal clinical trials in osteoarthritis were obtained under from the FDA under Freedom of Information (FOI). Although a direct comparison with other drugs is not possible and no drugs exist in the Tramadol class (combined serotonergic, noradrenergic and opioidergic effects), data on other analgesics provide a context for the results of the Tramadol ER study.



Rofecoxib (VIOXX®) is approved for the treatment of osteoarthritis at a daily dose of 12.5 mg; with the comment that some patients may derive a benefit from an increase in dose to 25 mg per day (maximum dose). The efficacy studies with rofecoxib in osteoarthritis were 6 weeks in duration. The WOMAC variable  
5 "pain walking on a flat surface" was used as the primary endpoint. In most cases, the LS mean change from baseline over 6-weeks formed the basis of comparison. The mean difference between rofecoxib 12.5 mg and placebo was 14.3 mm (Study No. 029), 12.4 mm (Study No. 033), 15.4 mm (Study No. 040) and 9.0 (Study No. 058). Similarly, the mean difference between the positive control  
10 and placebo was 13.5 mm (Ibuprofen, 2400 mg, Study No. 033), 14.6 mm (Ibuprofen, 2400 mg, Study No. 040) and 10 mm (Nabumetone [Relafen®], 1500 mg, Study No. 058).

Celecoxib (CELEBREX®) is approved for the treatment of osteoarthritis at a daily dose of 200 mg. Pivotal clinical trials were placebo controlled studies of  
15 either 6 or 12 weeks duration and used naproxen as the positive control. Study No. 020 and 054 served as pivotal clinical trials and Studies 040 and 087 were placebo controlled evaluations of celecoxib 100 mg BID vs. 200 mg QD. There were multiple primary endpoints in each of the studies, including Patients Assessment of Arthritis Pain VAS. The LS mean difference in pain VAS change  
20 from baseline between celecoxib 100 mg BID and placebo was 8.0 mm (12 weeks; Study No. 020), 12.2 mm (12 weeks; Study No. 054), 13.9 mm (6 weeks; Celecoxib 100 mg BID; Study No. 040) and 13.1 mm (6 weeks; Celecoxib 200 mg QD; Study No. 040), 6.2 mm (6 weeks; Celecoxib 100 mg BID; Study No. 087) and 8.5 mm (6 weeks; Celecoxib 100 mg BID; Study No. 087). Similarly, the mean difference  
25 between the positive control and placebo was 7.6 mm (Naproxen 500 mg BID, Study No. 020) and 11.2 mm (Naproxen 500 mg BID, Study No. 054).

The results of the present study demonstrate that Tramadol ER at an approximate dose of 300 mg QD (range 200 to 400 mg) provides a robust analgesic response in OA. The magnitude of the response is at least equal, if not  
30 superior to that of NSAIDs and COX-2 inhibitors. With its advantage of once

daily dosing, Tramadol ER will be an important addition to the therapeutic armamentarium of clinicians treating chronic pain.

EXAMPLE 11:

A double-blind, placebo-controlled, parallel-group comparison of the efficacy and safety of 200 mg and 300 mg Tramadol HCl Extended-Release Tablets to placebo in the treatment of chronic low back pain was conducted.

11.1: Study Overview

A multicenter, multiple-dose, randomized, placebo-controlled, parallel-group study involving a minimum of 360 patients designed to compare the analgesic efficacy and safety of extended release tramadol (Tramadol ER) 300 mg and 200 mg orally (PO) once-daily (QD) to placebo in patients with chronic low back pain.

11.2: Subjects

Patients with chronic ( $\geq 6$  months) low back pain requiring daily treatment with an analgesic.

11.3: Design

An open-label run-in period followed by a double-blind, randomized, multiple-dose, placebo-controlled study. Patients may roll-over into an ongoing 1-year open-label extension study.

11.4: Treatment Regimen:

A 3-week, open-label run-in period, including 2 weeks of dose titration on Tramadol ER, beginning with 100 mg, to attain a tolerable dose of 300 mg QD, followed by 1 week on a stable maintenance dose of Tramadol ER 300 mg QD. Following the run-in period, patients were randomized to one of the following double-blind treatments:

Tramadol ER 300 mg QD at 8:00 A.M.;

Tramadol ER 200 mg QD at 8:00 A.M.;

Placebo QD at 8:00 A.M.

11.5: Enrollment Period

5 months

### 11.6: Treatment Period

At Screening (Visit 1), eligible patients underwent laboratory testing, and then entered a 2 to 7 day washout period during which all analgesic use was discontinued. At Visit 2 (Week -3), eligible patients who reported a pain intensity of  $\geq 40$  mm on a visual analog scale entered a 3-week, open-label run-in period. Patients were initiated on Tramadol ER 100 mg QD and maintained at their dose for at least 3 days. On Day 4, and for the remainder of the week (until their return to the clinic for Visit 3, Week -2), patients had their dose increased to 200 mg QD, based on the tolerability of side effects. Beginning at Visit 3 (Week -2), patients were maintained on a minimum Tramadol ER dose of 200 mg QD, and the dose titrated upwards (i.e. to 300 mg QD) based on the tolerability of side effects. Beginning at Visit 4 (Week -1), patients escalated their Tramadol ER dose to 300 mg QD and maintained that dose for 1 week. No further dose adjustments were permitted during the remainder of the run-in period. In patients with pain unresponsive to appropriate dosage adjustments, or with unacceptable side effects, treatment was discontinued and alternate analgesic therapy initiated, as appropriate. Eligible patients receiving Tramadol ER 300 mg QD at the end of the 3-week run-in period were entered into a 12-week, double-blind, randomized study. At Visit 5 (Week 0), patients were randomly assigned to receive Tramadol ER 300 mg QD, Tramadol ER 200 mg QD, or placebo QD. Study medication dosing occurred daily at 8:00 A.M. No dose adjustments were permitted in the double-blind period. Patients unable to tolerate the double-blind study medication and those with unacceptable pain control were dropped from the study. Patients returned for efficacy and safety evaluations at Week 1 (Visit 6), Week 2 (Visit 7), Week 4 (Visit 8), Week 8 (Visit 9), and Week 12 (Visit 10), or Early Termination. Study medication was discontinued at Visit 10 and patients were treated with nonopioid analgesics until they returned to the clinic after 1 week for a post-study medication visit (Visit 11, Week 13). Patients were contacted by telephone between Visit 10 and Visit 11 to ensure that they were not taking opioid analgesics, including tramadol. Visit 11 was scheduled earlier than 1 week after Visit 10, in the event that patient pain could not be

managed with nonopioid analgesics, and intervention with opioid analgesics or tramadol was necessary. At Visit 11, patients completed assessments for physical dependence and adverse events.

11.7: No. of Centers

5           30 centers

11.8: No. of Subjects

Approximately 600 patients were enrolled to provide a minimum of 360 patients (120 patients per treatment).

11.9: Efficacy

10           At each visit, patients were asked to rate their current pain intensity and their pain intensity since their previous visit, using a visual analog scale (VAS), and they provided an overall global assessment of study medication. The primary efficacy measure was the patient's pain intensity VAS score since the previous visit. Secondary measures included the patient's current pain intensity,  
15           the patient's global assessment, the Roland Disability Index, the patient's assessment of sleep and premature study termination due to inefficacy.

11.10: Safety

Safety was assessed at each visit by vital signs (heart rate, respiratory rate, supine or sitting and standing blood pressure) and a non-directed adverse events  
20           questionnaire. At Screening and at each visit, including Early Termination, patients were evaluated for the occurrence of syncope, orthostasis, dizziness, drop attacks and flushing (vasodilation). Adverse events were monitored throughout the study. Physical examination was performed at Screening (Visit 1) and at the Final Visit (Visit 11), or at Early Termination. Clinical laboratory  
25           testing was performed at Screening (Visit 1), at Week -3 (Visit 2), at Baseline (Week 0, Visit 5), at Week 1 (Visit 6), and at Week 12 (Visit 10) or Early Termination. In females of childbearing potential, serum pregnancy tests were performed at Screening (Visit 1), at Week -3 (Visit 2), at Baseline (Week 0, Visit 5), at Week 1 (Visit 6), at Week 4 (Visit 8), at Week 8 (Visit 9), and at Week 12  
30           (Visit 10) or Early Termination. If the Screening (Visit 1) serum pregnancy results were not available from the central laboratory at the start of the run-in period

(Visit 2), then the site obtained a urine pregnancy test locally. EKGs were performed at Screening (Visit 1), at Baseline (Week 0, Visit 5) and at Week 12 (Visit 10) or at Early Termination. The Addiction Research Center Inventory (ARCI) Short-form was completed by patients at each visit following the  
5 Screening Visit. The Physical Dependence Questionnaire was completed by patients at the start of the run-in period (Visit 2), at Week 12 (Visit 10), and at Week 13 (Visit 11) or at Early Termination.

While the foregoing provides a detailed description of preferred embodiments of the present invention, it is to be understood that this description  
10 is only illustrative of the principles of the invention and is not limitative. Numerous modifications, variations and adaptations may be made to the particular embodiments of the invention described above without departing from the scope of the invention, which is defined in the claims.